

Original Article

The ERCC2 gene K751Q polymorphism contributes to cancer susceptibility in Chinese population: a meta-analysis of 40827 subjects

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Abstract: Associations between ERCC2 gene K751Q polymorphism and cancer risk have been evaluated in worldwide population and Indian population, but results are still unknown in Chinese population. We performed the present meta-analysis to derive a precise estimation of the associations in Chinese population. Systematic searches of electronic databases PubMed, Embase and Chinese Biomedical (CBM) databases, as well as hand searching of the references of identified articles were performed. Based on our search criteria, a total of 60 eligible articles containing 63 studies were included in the final meta-analysis, comprising 19044 cases and 21783 controls. Overall, significant association was found in all genetic models (for allelic model: OR = 1.23, 95% CI = 1.12-1.36, P = 0.000; for additive model: OR = 1.95, 95% CI = 1.73-2.19, P = 0.000; for dominant model: OR = 1.22, 95% CI = 1.10-1.35, P = 0.000; and for recessive model: OR = 1.80, 95% CI = 1.60-2.02, P = 0.000). The results suggested that the ERCC2 gene K751Q polymorphism was associated with the susceptibility to cancer in Chinese population. However, due to the high heterogeneity and publication bias in the meta-analysis, the results should be interpreted with caution.

Keywords: ERCC2, XPD, cancer, polymorphism, meta-analysis

Introduction

The excision repair cross-complementing rodent repair deficiency, complementation group 2 (ERCC2)/xeroderma pigmentosum complementary group D (XPD) protein, 761 amino acids in length, is considered to be a key enzyme in nucleotide excision repair (NER) pathway and plays an important role in the repair of DNA damages [1]. Several important single nucleotide polymorphisms have been identified in the ERCC2 locus. Among them, ERCC2 K751Q polymorphism (rs13181) is one of the most commonly studied polymorphisms. ERCC2 K751Q is an A to C mutation at the codon 751 of exon 23, resulting in an amino acid alteration from lysine (Lys [K]) to glycine (Gln [Q]) [2]. This SNP can give rise to repair and transcription defects, and altered DNA repair capacity can render a higher risk of developing different types of cancer [3].

Recently, numerous molecular epidemiological studies have evaluated the relationship be-

tween ERCC2 gene K751Q polymorphism and cancer susceptibility. However, the results remain conflicting rather than conclusive. Meta-analyses of studies in worldwide population [4, 5] and Indian population [6] have revealed significant associations of the ERCC gene K751Q polymorphism and cancer susceptibility; however, results are still unknown in Chinese population. Considering that genotype frequency of various polymorphic loci may manifest racial differences, we conducted a meta-analysis by collecting and sorting the previously published studies in Chinese population.

Materials and methods

Literature search and inclusion/exclusion criteria

We searched PubMed, Embase and Chinese Biomedical (CBM) databases for relevant articles (up to August 28, 2015). The search terms were as follows: ("excision repair cross-complementing rodent repair deficiency complementa-

tion group 2" OR "ERCC2" OR "xeroderma pigmentosum complementary group D" OR "XPD" OR "DNA repair gene") AND ("polymorphism" OR "mutation" OR "variant") AND ("cancer" OR "neoplasms"). The equivalent Chinese terms were applied in the Chinese databases. All eligible reports were restricted to English and Chinese language articles. Additionally, the reference lists of all identified studies and review articles were also screened.

Studies were included in the meta-analysis if they fulfilled the following criteria: (1) case-control studies focusing on association between the ERCC2 gene K751Q polymorphism and cancer susceptibility; (2) sufficient information provided to estimate odds ratios (ORs) and their 95% confidence intervals (CIs); (3) no overlapping data with other investigations. If studies had the same or overlapping data, only the largest study should be included in the final analysis. Studies were excluded based on the following criteria: animal studies, abstracts, reviews, case report, letters, editorials, comments and conference proceedings.

Data extraction

Two authors (Ma L and Zhang H) independently extracted data from all eligible studies. Disagreements would be discussed and resolved by the third author (Ma YQ). The following information was collected from each study: first author's surname, publication date, region and ethnicity (Han or Minority) of study population, source of controls (population-based [PB] study or hospital-based [HB] study), total numbers of cases and controls, and distribution of genotypes and alleles in cases and controls, respectively. Besides, evidence of Hardy-Weinberg equilibrium (HWE) was also collected.

Quality score assessment

Two authors (Ma L and Guo WZ) of this article independently assessed the quality of included studies using the Newcastle-Ottawa scale (NOS) [7]. The NOS ranges between zero and nine stars, and studies with a score of seven stars or greater were considered to be of high quality. Disagreement was settled as aforementioned.

Statistical analysis

We estimated the association between the ERCC2 gene K751Q polymorphism and cancer

risk based on four genetic models: allelic model (C allele versus A allele), additive model (C/C versus A/A), dominant model (C/C+A/C versus A/A), and recessive model (C/C versus A/C+A/A) [8].

The fixed-effects model was used when no inter-study heterogeneity was observed, otherwise the random-effects model was used [9, 10]. The Cochran's Q statistic and I^2 statistic were adopted to measure heterogeneity, $P < 0.10$ and $I^2 > 50\%$ indicated existence of heterogeneity [11, 12]. To detect the potential sources of heterogeneity, Galbraith plot was used. Subgroup analyses were performed based on cancer types (if one cancer type contained less than three individual studies, it was combined into the "other cancer" group), ethnicity (Chinese Han ethnic) and source of controls (PB and HB). Sensitivity analysis was conducted by limiting the meta-analysis to studies conforming to HWE ($P < 0.05$ of HWE was considered significant) and to the high quality studies (NOS score ≥ 7). In addition, publication bias was investigated with Begg's funnel plot and Egger's regression test (publication bias was considered to be statistically significant when $P < 0.05$) [13]. All the statistical analyses were performed using Stata 12.0 (Stata Corp LP, College Station, TX).

Results

Study characteristics

The study selection process is shown in the **Figure 1**. Based on our search criteria, a total of 60 eligible articles contained 63 studies were included in the final meta-analysis [14-73], comprising 19044 cases and 21783 controls. The characteristics of selected studies are presented in **Table 1**. Of the 63 studies, 11 investigated lung cancer, 10 investigated esophageal cancer, 9 investigated liver cancer, 6 investigated gastric cancer, 4 investigated breast cancer, 4 investigated colorectal cancer. Thirty-two of these studies were conducted in Chinese Han ethnic populations. Controls were PB in 8 studies and HB in 54 studies. In addition, the genotypes of control group showed significant deviation from HWE in 12 studies ($P < 0.05$) [28, 35, 36, 41, 42, 45, 47, 48, 62, 65, 67, 72]. The NOS results of 60 articles showed that the average score was 7.7, which indicated that the methodological quality was generally good.

ERCC2 gene K751Q polymorphism and cancer susceptibility

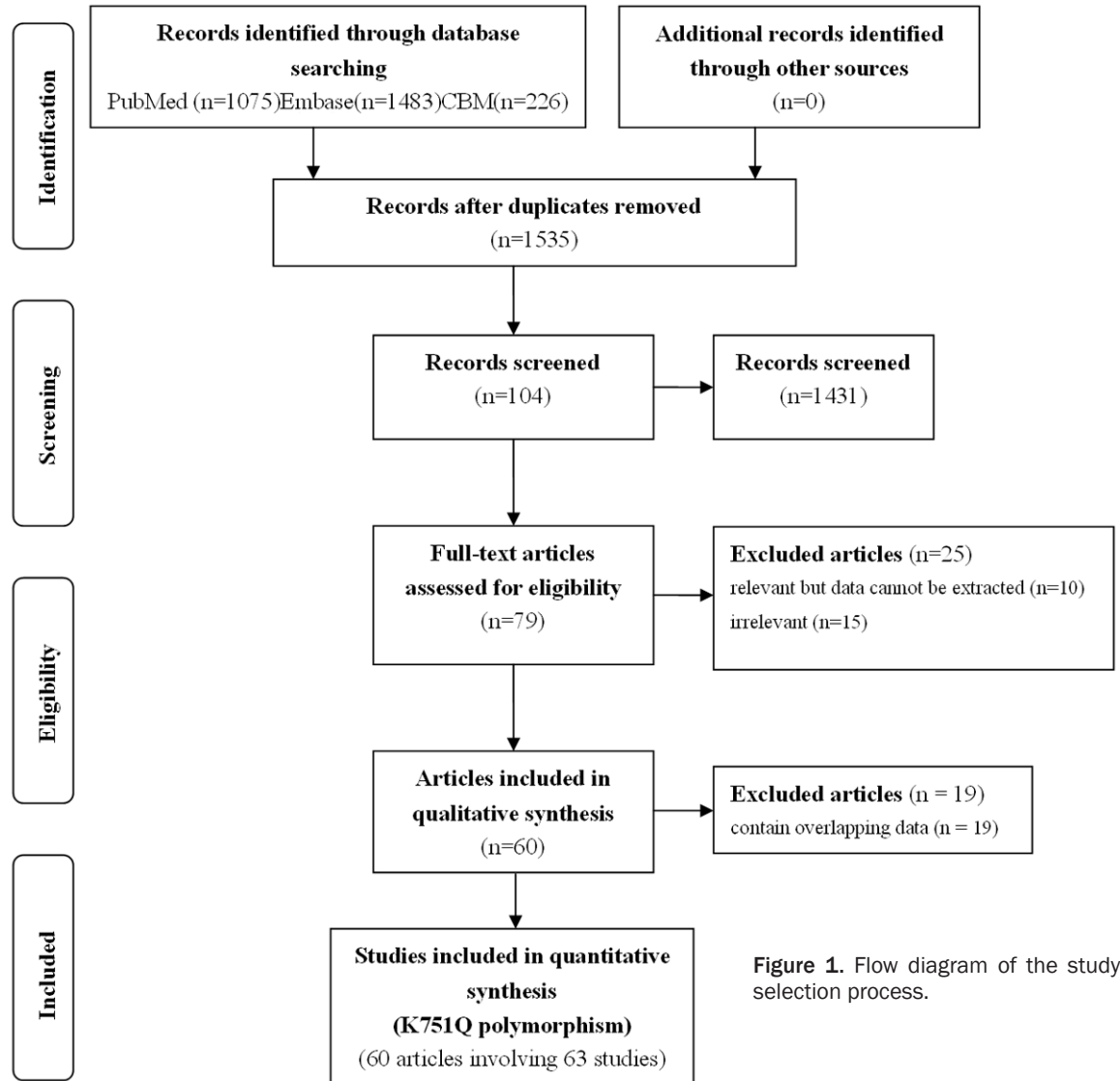


Figure 1. Flow diagram of the study selection process.

Quantitative synthesis

Results of pooled analysis on the association between the ERCC2 gene K751Q polymorphism and cancer susceptibility were shown in **Table 2**. Significant inter-study heterogeneity existed in the allelic model ($I^2 = 77.0\%$) and dominant model ($I^2 = 72.3\%$), but not in the additive model ($I^2 = 48.0\%$) and recessive model ($I^2 = 41.0\%$). Thus, we chose the random-effects model to synthesize the data of allelic model and dominant model, and used fixed-effects model to analyze the data of additive model and recessive model. Overall, significant association was found in all genetic models (for allelic model: OR = 1.23, 95% CI = 1.12-1.36, $P = 0.000$; for additive model: OR = 1.95, 95% CI

= 1.73-2.19, $P = 0.000$; for dominant model: OR = 1.22, 95% CI = 1.10-1.35, $P = 0.000$; and for recessive model: OR = 1.80, 95% CI = 1.60-2.02, $P = 0.000$). In the subgroup analysis by cancer types, significant association was found between the ERCC2 gene K751Q polymorphism and susceptibility to esophageal and liver cancer in all genetic models. But positive results were only obtained in additive and dominant models in subgroups of gastric and colorectal cancer, and in allelic and recessive models in lung cancer. No association was found in all genetic models in breast cancers. In the subgroup analysis by ethnicity, only the data of Han ethnic population was analyzed. It turned out that there was significant association between the ERCC2 gene K751Q polymor-

ERCC2 gene K751Q polymorphism and cancer susceptibility

Table 1. Characteristics of studies included in this meta-analysis

No.	First author	Year	Region	Ethnicity	Type of cancer	Source of controls	Sample size (case/control)	Genotype distribution (case/control)					HWE Y/N (p)	NOS score
								A/A	A/C	C/C	A	C		
1	Xing et al	2002	Beijing	Han	Esophageal cancer	PB	433/524	367/451	63/70	3/3	797/972	69/76	Y (0.874)	9
2	Chen et al	2002	Jiangsu	NA	Lung cancer	PB	109/109	51/41	47/48	11/20	149/130	69/88	Y (0.373)	9
3	Liang et al	2003	Beijing	Han	Lung cancer	PB	1006/1020	839/848	153/166	14/6	1831/1862	181/178	Y (0.488)	9
4	Xu et al	2004	Jiangsu	Han	Liver cancer	PB	70/136	57/125	13/10	0/0	127/260	13/12	Y (0.135)	9
5	Yu et al	2004	Hubei	Han	Esophageal cancer	HB	135/152	108/133	16/17	11/2	232/283	38/21	Y (0.108)	8
6	Yeh et al	2005	Taiwan	NA	Colorectal cancer	HB	727/736	622/631	112/96	3/4	1356/1358	118/104	Y (0.866)	8
7	Zhang et al	2005	Henan	NA	Breast cancer	HB	220/310	74/99	112/165	34/46	260/363	180/257	Y (0.089)	7
8	Yin et al	2005	Jiangsu	Han	Esophageal cancer	HB	106/106	91/95	14/11	1/0	196/201	16/11	Y (0.573)	7
9	Chen et al	2005	Taiwan	NA	Liver cancer	PB	570/381	496/322	72/55	2/4	1064/699	76/63	Y (0.346)	9
10	Liang et al	2006	Shanghai	Han	Biliary tract cancer	PB	443/448	369/383	69/63	5/2	807/829	79/67	Y (0.730)	9
11	Hu et al	2006	Mix	Han	Lung cancer	HB	975/997	827/865	141/127	7/5	1795/1857	155/137	Y (0.884)	8
12	Lou et al	2006	Liaoning	Han	Gastric cancer	HB	238/200	205/164	30/33	3/3	440/361	36/39	Y (0.377)	7
13	Zhoua et al	2007	Hebei	Han	Esophageal cancer	HB	327/612	274/522	51/86	2/4	599/1130	55/94	Y (0.824)	8
14	Zhoub et al	2007	Hebei	Han	Gastric cardiac cancer	HB	253/612	224/522	26/86	3/4	474/1130	32/94	Y (0.824)	8
15	Yang et al	2007	Sichuan	Han	Nasopharyngeal cancer	HB	153/168	128/124	24/43	1/1	280/291	26/45	Y (0.181)	7
16	Bau et al	2007b	Taiwan	NA	Prostate cancer	HB	123/479	111/441	10/33	2/5	232/915	14/43	N (<0.001)	7
17	Shao et al	2007	Jiangsu	Han	Bladder cancer	HB	215/245	167/211	47/32	1/2	381/454	49/36	Y (0.525)	8
18	Bau et al	2007a	Taiwan	NA	Oral cancer	HB	154/105	134/89	18/15	2/1	286/193	22/17	Y (0.682)	7
19	Song et al	2008	Shandong	Han	Non-Hodgkin's Lymphoma	HB	309/305	261/270	43/32	5/3	565/572	53/38	Y (0.075)	7
20	Chen et al	2008	Jiangsu	NA	Esophageal cancer	PB	321/392	237/311	79/76	5/5	553/698	89/86	Y (0.884)	9
21	Yin et al	2008	Liaoning	Han	Lung cancer	HB	239/236	213/217	25/19	1/0	451/453	27/19	Y (0.519)	7
22	Li et al	2008	Shanghai	Han	Breast cancer	HB	486/479	432/392	51/80	3/7	915/864	57/94	Y (0.218)	8
23	Kong et al	2008	Shandong	Han	Lung cancer	HB	114/114	96/101	13/9	5/4	205/211	23/17	N (<0.001)	7
24	He et al	2008	Zhejiang	NA	Cervical cancer	HB	134/200	105/164	27/31	2/5	237/359	31/41	N (0.026)	8
25	Zeng et al	2009	Guangxi	Mix	Liver cancer	HB	300/312	263/270	32/39	5/3	558/579	42/45	Y (0.244)	8
26	Yang et al	2009	Mix	NA	Non-Hodgkin's Lymphoma	HB	72/354	64/304	7/48	1/2	135/656	9/52	Y (0.944)	7
27	Wang et al	2009	Liaoning	Han	Colon cancer	HB	170/200	143/164	19/33	8/3	305/361	35/39	Y (0.377)	7
28	Zhai et al	2009	Henan	Han	Esophageal cancer	HB	200/200	167/148	31/51	2/1	365/347	35/53	Y (0.122)	8
29	Chang et al	2009	Taiwan	NA	Bladder cancer	HB	308/308	280/278	21/22	7/8	581/578	35/38	N (<0.001)	8
30	Long et al	2009	Guangxi	Mix	Liver cancer	HB	618/712	272/464	222/187	124/61	766/1115	470/309	N (<0.001)	8
31	Yin et al	2009	Liaoning	Han	Lung cancer	HB	285/285	220/242	61/40	4/3	501/524	69/46	Y (0.361)	8
32	Tian et al	2010	Guizhou	NA	Laryngeal Carcinoma	HB	72/72	34/30	35/36	3/6	103/96	41/48	Y (0.289)	7
33	Ma et al	2010	Heilongjiang	Han	Lung cancer	PB	222/222	128/194	62/24	32/4	318/412	126/32	N (0.004)	8
34	Ming-Shiean et al	2010	Taiwan	NA	Breast cancer	HB	401/533	334/450	60/77	7/6	728/977	74/89	Y (0.196)	8
35	Wang et al	2010	Taiwan	NA	Breast cancer	HB	1232/1433	1136/1316	81/96	15/21	2353/2728	111/138	N (<0.001)	8

ERCC2 gene K751Q polymorphism and cancer susceptibility

36	Long et al	2010	Guangxi	Mix	Gastric cancer	HB	361/616	139/400	151/164	71/52	429/964	293/268	N (<0.001)	8
37	Cui et al	2010	Liaoning	NA	Liver cancer	HB	94/111	69/97	24/14	1/0	162/208	26/14	Y (0.478)	7
38	Xiao et al	2010	Guizhou	NA	Acute leukemia	NA	100/100	83/90	16/10	1/0	182/190	18/10	Y (0.599)	7
39	Chen et al	2011	Mix	NA	Gastric cancer	HB	208/339	166/282	40/55	2/2	372/619	44/59	Y (0.698)	7
40	Qian et al	2011	Tianjing	Han	Lung cancer	HB	580/601	477/507	97/87	6/7	1051/1101	109/101	Y (0.144)	8
41	Ma et al	2011	Gansu	Han	Cervical cancer	HB	200/200	172/167	28/31	0/2	372/365	28/35	Y (0.678)	7
42	Wang et al	2011	Taiwan	NA	Urothelial Carcinoma	HB	460/540	390/472	70/67	0/1	850/1011	70/69	Y (0.386)	8
43	Huang et al	2012	Xinjiang	Mix	Esophageal cancer	HB	213/358	150/274	55/79	8/5	355/627	71/89	Y (0.796)	8
44	Wang et al	2012	Henan	Han	Esophageal cancer	HB	405/405	264/289	115/100	26/16	643/678	167/132	Y (0.056)	8
45	Wu et al	2012	Henan	Han	Esophageal cancer	HB	235/235	136/142	86/79	13/14	358/363	112/107	Y (0.499)	8
46	Chen et al	2012	Hubei	NA	Glioma	HB	393/410	139/175	198/186	56/49	476/536	310/284	Y (0.969)	7
47	Zhou et al	2012	Shanghai	NA	Lung cancer	HB	103/103	86/87	17/16	0/0	189/190	17/16	Y (0.393)	7
48	Guo et al	2012	Liaoning	NA	Liver cancer	HB	410/410	190/233	183/159	37/18	563/625	257/195	Y (0.158)	8
49	Jianga et al	2012	Henan	Han	Gastric cancer	HB	98/80	49/54	32/20	17/6	130/128	66/32	Y (0.050)	7
50	Jiangb et al	2012	Henan	Han	Liver cancer	HB	76/80	32/54	26/20	18/6	90/128	62/32	Y (0.050)	7
51	Jiangc et al	2012	Henan	Han	Colorectal cancer	HB	95/80	55/54	24/20	16/6	134/128	56/32	Y (0.050)	7
52	Tian et al	2013	Guangdong	Han	Laryngeal carcinoma	HB	233/102	179/81	39/15	15/6	397/177	69/27	N (<0.001)	7
53	Ouyang et al	2013	Hunan	Han	Lung cancer	HB	82/201	68/167	14/34	0/0	150/368	14/34	Y (0.190)	7
54	Ni et al	2014	Jiangsu	NA	Colorectal cancer	HB	213/240	176/201	35/38	2/1	387/440	39/40	Y (0.573)	8
55	Lu et al	2014	Henan	NA	Laryngeal Carcinoma	HB	176/176	85/94	60/56	31/26	230/244	122/108	N (<0.001)	8
56	Wu et al	2014	Hainan	NA	Hepatocellular carcinoma	HB	218/277	105/156	93/111	20/10	303/423	133/131	Y (0.068)	7
57	Wang et al	2014	Hebei	NA	gastric cancer	HB	300/300	96/99	114/177	90/24	306/375	294/225	N (<0.001)	7
58	Hui et al	2014	Henan	NA	glioma	HB	138/276	72/158	56/106	10/12	200/422	76/130	Y (0.269)	8
59	Li et al	2014	Beijing	Han	Non-Hodgkin's Lymphoma	HB	282/231	240/194	37/34	5/3	517/422	47/40	Y (0.291)	7
60	Zhu et al	2014	Shanghai	Han	esophageal cancer	HB	1122/1111	937/954	175/149	10/8	2049/2057	195/165	Y (0.413)	8
61	Zhu et al	2014	Jiangsu	Han	bladder cancer	HB	287/282	233/220	50/58	4/4	516/498	58/66	Y (0.936)	7
62	Du et al	2014	Shanghai	NA	lung cancer	HB	120/120	78/96	24/16	18/8	180/208	60/32	N (<0.001)	7
63	Zhao et al	2014	Qinghai	Tibetan	Hepatocellular carcinoma	HB	102/102	80/91	20/11	2/0	180/193	24/11	Y (0.565)	8

PB, population-based; HB, hospital-based; HWE, Hardy-Weinberg equilibrium; Y, yes; N, no.

ERCC2 gene K751Q polymorphism and cancer susceptibility

Table 2. Meta-analysis of ERCC2 gene K751Q polymorphism and cancer risk in each subgroup

Category	Study (n)	Sample size (case/control)	C versus A		C/C versus A/A		C/C+A/C versus A/A		C/C versus A/C+A/A	
			OR (95% CI)	I ² (%)	OR (95% CI)	I ² (%)	OR (95% CI)	I ² (%)	OR (95% CI)	I ² (%)
Overall	63	19044/21783	1.23 [1.12, 1.36] ^a	77.0	1.95 [1.73, 2.19]	48.0	1.22 [1.10, 1.35] ^a	72.3	1.80 [1.60, 2.02]	41.0
<i>SA based on cancer types</i>										
Lung cancer	11	3835/4008	1.38 [1.03, 1.86] ^a	84.5	1.79 [0.88, 3.63] ^a	69.9	1.39 [1.04, 1.85] ^a	79.3	1.69 [0.89, 3.20] ^a	64.1
Esophageal cancer	10	3497/4095	1.20 [1.08, 1.33]	42.5	1.65 [1.17, 2.32]	0.0	1.19 [1.06, 1.33]	28.6	1.57 [1.12, 2.22]	0.0
Liver cancer	9	2458/2521	1.62 [1.22, 2.15] ^a	81.4	3.00 [2.33, 3.87]	20.9	1.66 [1.21, 2.26] ^a	78.8	2.47 [1.93, 3.16]	0.0
Gastric cancer	6	1458/2147	1.38 [0.94, 2.02] ^a	87.3	3.45 [2.58, 4.61]	0.8	1.29 [0.77, 2.16] ^a	89.4	3.13 [2.38, 4.11]	35.0
Breast cancer	4	2399/2755	0.88 [0.69, 1.13] ^a	66.4	0.91 [0.63, 1.32]	0.0	0.86 [0.66, 1.13] ^a	59.8	0.95 [0.67, 1.36]	0.0
Colorectal cancer	4	1205/1256	1.19 [0.98, 1.44]	0.0	2.11 [1.09, 4.09]	0.0	1.13 [0.92, 1.40]	0.0	2.09 [1.09, 4.03]	0.0
<i>SA based on ethnicity</i>										
Han	32	10074/10869	1.21 [1.05, 1.40] ^a	75.4	1.87 [1.51, 2.31]	22.9	1.18 [1.02, 1.36] ^a	71.1	1.77 [1.43, 2.19]	10.2
<i>SA based on source of controls</i>										
HB	54	15770/18451	1.22 [1.11, 1.35] ^a	73.8	1.96 [1.73, 2.22]	41.0	1.20 [1.08, 1.34] ^a	69.3	1.81 [1.61, 2.04]	33.9
PB	8	3174/3232	1.31 [0.90, 1.92] ^a	89.2	1.48 [0.58, 3.81] ^a	75.2	1.33 [0.92, 1.92] ^a	86.0	1.44 [0.61, 3.40] ^a	70.7
<i>Sensitivity analysis</i>										
BH	51	15103/17001	1.15 [1.06, 1.25] ^a	55.4	1.53 [1.31, 1.79]	7.4	1.14 [1.07, 1.20]	49.5	1.44 [1.24, 1.68]	0.0

OR, odds ratio; CI, confidence interval; SA: Subgroup analysis; HB, hospital-based; PB: population-based. BH: based on HWE (studies without HWE were excluded). ^aSignificant heterogeneity: the random-effects model was chosen to summarize the results.

ERCC2 gene K751Q polymorphism and cancer susceptibility

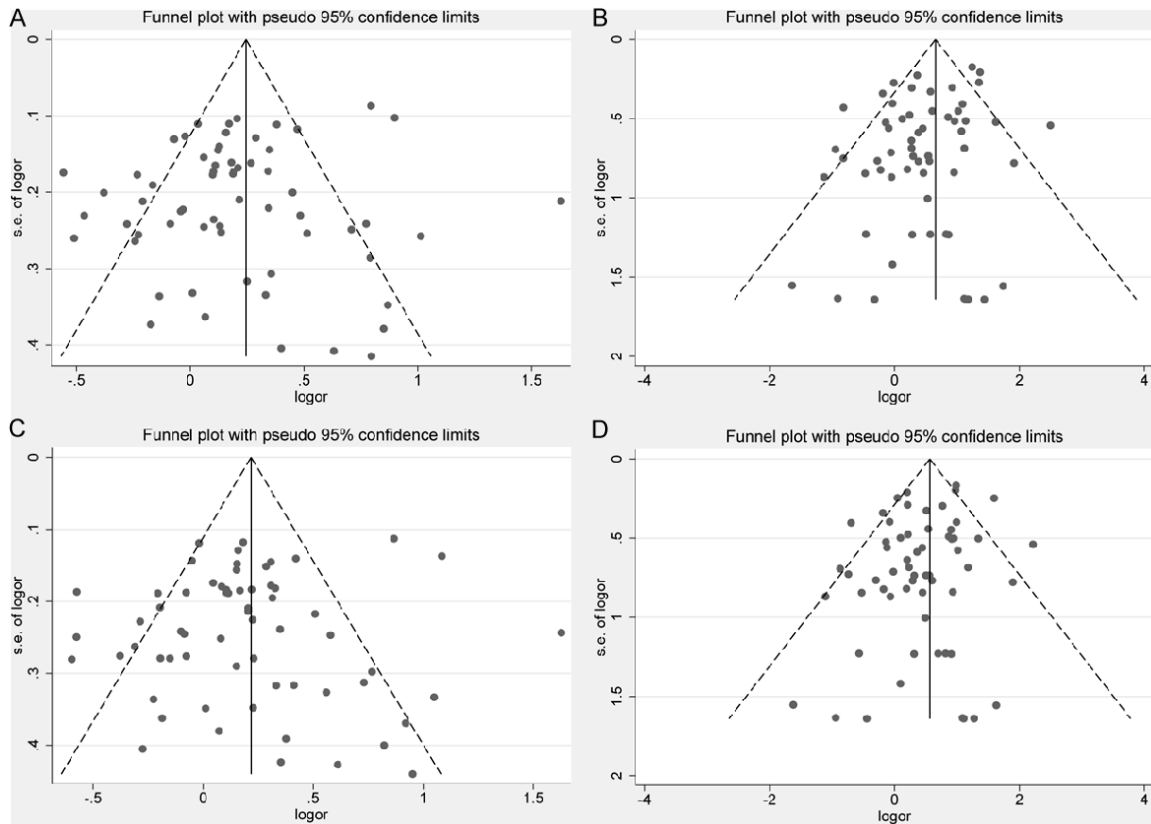


Figure 2. Funnel plots for ERCC2 gene K751Q polymorphisms and cancer risk. A (allelic model: C allele vs. A allele); B (additive model: C/C vs. A/A); C (dominant model: C/C+A/C vs. A/A); D (recessive model: C/C vs. A/C+A/A).

phism and cancer susceptibility in all genetic models. When stratified by source of controls, a positive result was obtained in all genetic models in the HB subgroup. But no significant association was found in the PB subgroup.

Heterogeneity analysis

In the present meta-analysis, significant inter-study heterogeneity existed in the allelic model and dominant model. To clarify the sources of heterogeneity, we conducted the subgroup analysis and sensitivity analysis. However, heterogeneity was not effectively removed. We further created a Galbraith plot to graphically assess the sources of heterogeneity. A total of 11 studies [15, 22, 27, 34, 40, 42, 45, 47, 48, 61, 72] were identified as the main sources of heterogeneity (10 studies [15, 22, 27, 40, 42, 45, 47, 48, 61, 72] for the allelic model; 7 studies [27, 34, 40, 42, 45, 48, 61] for the dominant model). After the outlier studies were excluded, the heterogeneity was effectively removed (for allelic model: $I^2 = 37.9\%$; for domi-

nant model: $I^2 = 20.7\%$) while the corresponding pooled ORs were not materially altered in all comparisons (for allelic model: OR = 1.19, 95% CI = 1.13-1.25, $P = 0.000$; for dominant model: OR = 1.17, 95% CI = 1.10-1.23, $P = 0.000$).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by removing studies that did not conform to HWE. The corresponding pooled ORs were not materially altered, indicating that our results were statistically convincing. The results of sensitivity analysis were shown in **Table 2**.

Publication bias of selected literatures was assessed by performing the Begg's funnel plot and Egger's regression test. The effect size was asymmetrically distributed with publication bias visually present (for additive model), shown in **Figure 2B**. The results of Egger's regression test also provided statistical evidence for publication bias ($P = 0.018$ for additive model). No obvious asymmetry was observed in other

ERCC2 gene K751Q polymorphism and cancer susceptibility

genetic models according to the visual assessment of funnel plot (**Figure 2**). In addition, no statistical evidence for publication bias in Egger's regression test ($P = 0.199$ for allelic model; $P = 0.499$ for dominant model; $P = 0.067$ for recessive model).

Discussion

Cancer is one of multifactorial diseases and is due in part to abnormal gene function [74]. The association between ERCC2 gene K751Q polymorphism and cancer susceptibility has been widely studied. However, results in different studies have been inconsistent. In Chinese population, most studies showed that there were no significant associations between ERCC2 gene K751Q polymorphism and cancer susceptibility. Some study demonstrated that ERCC2 gene K751Q polymorphism was associated with developing cancer [17, 18, 29, 42, 43, 45, 48, 49, 58, 60, 61, 72, 73]. In addition, some study revealed that the ERCC2 gene-K751Q polymorphism was significantly associated with a protective effect of developing cancer [27, 34, 40]. Those controversial results may be due to the limitations of individual studies, such as the small size and low statistic power. To better understand the association between ERCC2 gene K751Q polymorphism and cancer risk, a meta-analysis with larger sample is necessary.

The present meta-analysis focused on only Chinese populations and included 19044 cancer cases and 21783 controls. The pooled results suggested that there was a significant association between ERCC2 gene K751Q polymorphism and susceptibility to cancer under all genetic models, which suggested that the C allele was associated with an increased risk of cancer in Chinese population. The result of the allelic model showed that the risk of developing cancer in C allele carriers was 1.23-fold higher than in those with the A allele. Furthermore, individuals with the C/C genotype had a significantly higher risk for developing cancer (OR = 1.95 in the additive model and OR = 1.80 in the recessive model) compared to those with the A/C or A/A genotype. Moreover, the result of the dominant model suggested that the risk of developing cancer in C allele carriers was 1.22-fold higher than in those with the A/A genotype.

In the subgroup analysis by cancer types, the results indicated that ERCC2 gene K751Q polymorphism was associated with increased risk of esophageal and liver cancer. Moreover, we found that the polymorphism was also associated with increased risk in subgroups of gastric and colorectal cancer (for C/C vs. A/A genotype and for C/C vs. A/C+A/A genotype), and lung cancer (for C allele vs. A allele and for C/C+A/C vs. A/A genotype). However, no association was found in breast cancer. The exact mechanism for the varying association between different tumor types and ERCC2 gene-K751Q polymorphism is still unknown, and it is suspected that ERCC2 genetic variants may exert different effects in different cancer types.

When stratified by ethnicity, ERCC2 gene K751Q polymorphism was also associated with increased risk of cancer among Chinese Han ethnic populations. Subgroup analyses by source of controls indicated that ERCC2 gene K751Q polymorphism was associated with an increased risk of cancer in the HB subgroups; while no significant association was found in the PB subgroup. The diverse results might be due to differences in interactions between complex gene-environment, different control matching criteria and selection biases. Furthermore, considering that the results produced from genetic association case-control studies may be inconvincible when the genotype distribution of controls does not conform to HWE [75], we performed sensitivity analysis by removing studies deviating from HWE, and similar results to that of the overall study were obtained. The results of subgroup and sensitivity analyses further strengthened the conclusion that the ERCC2 gene K751Q polymorphism contributed to increased risk of cancer.

Significant inter-study heterogeneity existed in the allelic model and dominant model, which may potentially affect the interpretation of the overall results. Heterogeneity may attribute to differences in sample-sizes, cancer types, ethnicity, control sources or the interaction with other risk factors. Herein, we performed subgroup and sensitivity analyses to further explore the sources of heterogeneity. However, heterogeneity still could not be fully removed. Therefore, we created a Galbraith plot to assess the heterogeneity and to identify potential outlier studies. A total of 11 studies were identified

as the main contributors to heterogeneity. After excluding the outlier studies, the above-mentioned heterogeneity was effectively removed while the corresponding pooled ORs were not materially altered, indicating that the overall results of this meta-analysis were statistically robust.

To better interpret our results, some limitations of this study could not be ignored. First, publication bias existed in the present meta-analysis, which might influence the interpretation of our final results supporting the role of the ERCC2 gene K751Q polymorphism in cancer risk in Chinese population. Asymmetrical “missing” data, which was in the right part of the funnel plot, suggested that the positive results of studies between ERCC2 gene K751Q polymorphism and cancer risk in the additive model may be unreported or unpublished. Second, significant inter-study heterogeneity was found in this meta-analysis. Although we identified that the outlier studies were the main contributors to heterogeneity according to Galbraith plot, heterogeneity was still an inevitable problem that may affect the precision of overall results. Third, only the unadjusted ORs and CIs were used in the present meta-analysis. Moreover, some methodological deficiencies of meta-analysis are inevitable, such as their retrospective nature that limited our further evaluation of the effects of the gene-gene and gene-environment interactions in cancer development.

In conclusion, this meta-analysis indicated that the ERCC2 gene K751Q C allele was associated with an increased risk of cancer in Chinese population. The SNP in this locus may be a candidate biomarker of cancer susceptibility in Chinese population. However, the result should be interpreted with caution due to its limitations.

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Disclosure of conflict of interest

None.

Authors' contribution

ZH and ML participated in the study design. All authors provided study material and were

involved in the manuscript writing. All read and approved the final manuscript.

Abbreviations

SNP, single nucleotide polymorphism; ERCC2, the excision repair cross-complementing rodent repair deficiency, complementation group 2; XPD, xeroderma pigmentosum complementary group D; NER, nucleotide excision repair; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; CBM, Chinese Biomedical; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; PB, population-based; HB, hospital-based; NOS, Newcastle-Ottawa Scale.

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