REVIEW

Association between Polymorphisms of ERCC5 Gene and Susceptibility to Gastric Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: several epidemiological studies have suggested that polymorphisms of the Excision Repair Cross Complementing Group-5 (ERCC5) gene might be related to gastric cancer risk; however, the results have been inconsistent or controversial. Therefore, we have performed a systematic review and meta-analysis to clarify the association between the ERCC5 gene polymorphisms and gastric cancer risk. **Materials and Methods:** An electronic search was conducted of several databases, including PubMed, Web of Science, and Google Scholar for articles that describe the association between polymorphisms of the ERCC5 gene and susceptibility of gastric cancer. **Results:** A total of 33 case control studies in 15 publications were included in the present meta-analysis. There were significant associations between gastric cancer susceptibility and ERCC5 gene rs751402 C>T (T vs. C: OR = 1.166, 95% C = 1.066-1.274, p= 0.001; TT vs. CC: OR = 0.723, 95% CI = 0.587-0.890, p = 0.002; TT+TC vs. CC: OR = 0.853, 95% CI = 0.757-0.961, p = 0.009; TT vs. TC+CC: OR = 0.793, 95% CI = 0.659-0.955, p = 0.015), rs2296147 T>C (C vs. T: OR = 1.268, 95% C = 1.049-1.532, p= 0.014), rs873601 G>A polymorphisms (A vs. G, OR = 1.087, 95% C = 1.021-1.159, p= 0.010; AA vs. GG, OR = 1.184, 95% CI = 1.043-1.343, p = 0.009, AA vs. AG+GG, OR = 1.156, 95% CI = 1.040-1.284, p = 0.007), but not rs2094258 C>T and rs1047768 T>C. **Conclusion:** the current meta-analysis demonstrates that rs751402 C>T, rs2296147 T>C, and rs873601 G>A polymorphisms of ERCC5 gene are associated with the susceptibility of gastric cancer.

Keywords: Gastric cancer- ERCC5 gene- polymorphism- susceptibility- Meta-analysis

Asian Pac J Cancer Prev, **18 (10)**, 2611-2617

Introduction

Gastric cancer is the 4th most common and 2th leading cause of cancer-associated mortality, accounting for 10.4% of all cancer deaths worldwide (Yaghoobi et al., 2017). Gastric cancer remains highly prevalent and accounts for a notable proportion of global cancer mortality. It is estimated that nearly 951,000 new gastric cancer cases and 723,000 deaths were occurred in 2012 (Ferlay et al., 2012; Torre et al., 2015). Despite the observed declines in the gastric cancer incidence, it causes one of the highest cancer burdens, as measured by disability-adjusted life years lost in several Asian and Central and South American (CSA) countries (Karimi et al., 2014; Sierra et al., 2016). It is well established that a number of risk factors including dietary and nutritional aspects, genetic predisposition and sporadically-occurring mutations, and Helicobacter pylori infection predispose to the development of gastric cancer 6-8. It has been estimated that 10% of gastric cancer cases show familial clustering; however, inherited component contributes to 1-3% of gastric cancers (Oliveira et al., 2004; Sierra et al., 2016).

The excision repair cross complementing group 5 (ERCC5) gene (also known as XPG; UVDR; XPGC; COFS3; ERCM2; ERCC5-201) is located on the human chromosome 13q32-33, which encodes a single-strand specific DNA endonuclease that makes the 3' incision in DNA excision repair following UV-induced damage (Kiyohara et al., 2007; Ma et al., 2012; Wang et al., 2013). ERCC5 (XPG DNA repair endonuclease) gene is an indispensable component of the nucleotide-excision repair (NER) pathway, which belongs to the flap structure-specific endonuclease 1 (FEN1) family (Kiyohara et al., 2007; Wang et al., 2013). ERCC5 is one

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of the main genes activated by p53 and are involved in DNA repair (Kannan et al., 2000; Neamatzadeh et al., 2015). Mutations in the ERCC5 gene cause either the cancer-prone disorders Xeroderma Pigmentosum (XP), a skin disorder characterized by hypersensitivity to UV light and increased susceptibility for skin cancer following UV exposure, or the severe neurodevelopmental disorder Cockayne syndrome (CS) (Ma et al., 2012; Wang et al., 2013). There is considerable evidence that some single nucleotide polymorphisms (SNPs) of ERCC5 gene are correlated to gastric cancer occurrence. However, the associations between ERCC5 gene polymorphisms and gastric cancer risk were still conflicting. Therefore, in the present systematic review and meta-analysis the association between polymorphisms of ERCC5 gene and gastric cancer susceptibility were comprehensively estimated.

Materials and Methods

Study Identification and Selection

A computerized literature search was conducted for the relevant available studies published in PubMed, Web of Science, EMBASE, and Google scholar. The literature search was updated on May 15, 2017. The search strategy identified all possible studies using combinations of the following keywords: ‘‘excision repair cross complementing group 5 gene’’, ‘’ERCC5 gene’’, ‘’XPG gene’’, ‘’rs751402 C>T’’, ‘’rs2296147 T>C’’, ‘’rs873601 G>A’’, ‘’rs2094258 C>T’’, ‘’rs1047768 T>C’’, ‘‘polymorphism’’, ‘‘genotype’’, ‘‘variant’’, ‘’mutation’’, ‘’gastric cancer’’, and ‘’stomach cancer’. The reference lists of retrieved publications, review articles and previous meta-analyses, were also hand-searched for collecting other relevant studies that was missed in the electronic search.

Eligibility Criteria

The following inclusion criteria were used in selecting literature for the current meta-analysis: (1) evaluation of the association between ERCC5 gene polymorphisms and gastric cancer; (2) studies with a case–control or cohort design; (3) sufficient published data for calculating odds ratios (ORs) with their 95% confidence intervals (95% CIs); and (4) studies published in English or Chinese. If multiple studies from the same case series were available, the one including the most individuals was used in the analysis. We excluded the studies if they were: (1) only abstracts, review articles, case reports, or editorials; (2) conducted on animals; (3) not designed as case-control or cohort studies; (3) not offering the essential data; (4) control population including gastric cancer patients or other disorders; (5) duplicate of previous publications.

Data Extraction

Data were independently extracted by two authors and then examined by an expert in headaches. From each of the included articles the following data were collected: first author, year of publication, country origin, ethnicity, total number of cases and controls, the frequencies of genotypes in case and control groups, minor allele frequencies (MAFs), P-value for Hardy–Weinberg equilibrium (HWE). In case of disagreement, consensus was obtained on every item by joint review of the study.

Statistical Analyses

The strength of association between ERCC5 gene polymorphisms and risk of gastric cancer was measured by odds ratios (ORs) and 95% confidence intervals (CIs) under five genetic models. Additionally, the strength of associations was assessed by using ORs and 95% CIs and the significance of pooled ORs was examined by Z test. Heterogeneity between studies was evaluated by Q test and I2 statistics. $P < 0.10$ or $I2 > 50\%$ indicated significant heterogeneity (Khoram-Abadi et al., 2016; Mehdinejad et al., 2017; Neamatzadeh et al., 2015). If substantial heterogeneity was detected, the random effects model (DerSimonian-Laird method) was used; otherwise the fixed effects model (the Mantel-Haenszel method) was utilized (DerSimonian et al., 1986). Hardy-Weinberg equilibrium (HWE) tests for the ERCC5 gene polymorphisms in the control groups were examined using chi-square test. If P value > 0.05, the genotype distribution of the control group conformed to HWE. Sensitivity analysis was conducted to assess the stability of the current meta-analysis results, namely, a single study in the present meta-analysis was omitted each time to reflect the influence of the individual data set to the pooled OR. Furthermore, to explore the source of between-study heterogeneity, the sensitivity analysis was performed by omission of studies deviated from HWE (Sadeghiyeh et al., 2017). Publication bias was examined using both qualitative Begg’s funnel plot and quantitative Egger test were used to assess publication bias and the significance level was set at 0.05 for both (Begg et al., 1994; Egger et al., 1997). All the statistical analyses were performed by comprehensive meta-analysis (CMA) version 2.0 software (Biostat, USA). All p-values were two-tailed with a significant level at 0.05.

Results

Study Characteristics

Initially, we have identified 28 publications through the database search. After reading the titles and abstracts, three publications with duplicate titles and four articles that were review articles or assessed unrelated diseases were excluded. Finally, a total of 33 case-control studies in 15 publications were identified met our inclusion criteria. Of those, there were ten case–control studies (Chen et al., 2016; Duan et al., 2015; Feng et al., 2016; Guo et al., 2016; He et al., 2012; Hua et al., 2016; Li et al., 2016; Lu et al., 2016; Yang et al., 2016; Zhou et al., 2016) with 4664 cases and 5150 controls concerning rs751402 C>T polymorphism, seven case–control studies (Chen et al., 2016; Feng et al., 2016; He et al., 2012; Hua et al., 2016; Lu et al., 2016; Yang et al., 2016; Yang et al., 2012) with 3812 cases and 4177 controls concerning rs2094258 C>T polymorphism, six case–control studies (Bai et al., 2016; He et al., 2012; Hua et al., 2016; Hussain et al., 2009; Li et al., 2014; Li et al., 2016) with 3064 cases and 3413 controls concerning rs1047768 T>C polymorphism, five

case–control studies (Chen et al., 2016; Duan et al., 2015; He et al., 2012; Hua et al., 2016; Yang et al., 2016) with 3699 cases and 3890 controls concerning rs2296147 T>C polymorphism, and five case–control studies (Chen et al., 2016; He et al., 2012; Hua et al., 2016; Zhou et al., 2016; Yang et al., 2016) with 3727 cases and 3918 controls concerning rs873601 G>A polymorphism. The alleles and genotypes distribution for ERCC5 gene polymorphisms in case group and control group of all studies were included in Table 1. The genotypes distribution frequencies among the controls were in agreement with HWE for all included articles except for three case-control studies (Table 1).

Quantitative Synthesis Results

The meta-analysis findings of the correlation between ERCC5 gene polymorphisms and gastric cancer risk are summarized in Table 2 and Figure 1. The pooled results based on all included studies not showed a significant association between rs751402 C>T polymorphism and gastric cancer risk under the allele model (T vs. C: OR = 1.166, 95% C = 1.066-1.274, p= 0.001), the homozygote model (TT vs. CC: OR = 0.723, 95% CI = 0.587-0.890, p = 0.002), the dominant model (TT+TC vs. CC: OR = 0.853, 95% CI = 0.757-0.961, p = 0.009), the recessive model (TT vs. TC+CC: OR = 0.793, 95% CI = 0.659-0.955, p = 0.015), but not under the heterozygote model (TC vs. CC: OR =

Table 1. Characteristics of Studies Included in XPG Polymorphisms and Gastric Cancer

First Author	Country	Case/ Control	Cases					Controls					MAFs	HWE
	(Ethnicity)		Genotypes			Allele		Genotypes			Allele			
rs751402 C>T			CC	TC	TT	C	T	CC	TC	TT	C	T		
Duan et al., 2012	China (Asian)	400/400	47	181	172	525	275	29	165	206	577	223	0.278	0.605
He et al., 2012	China (Asian)	1125/1196	148	491	486	1463	787	137	499	560	1619	773	0.323	0.11
Chen et al., 2016	China (Asian)	692/771	93	313	286	885	499	89	331	351	1033	509	0.33	0.416
Guo et al., 2016	China (Asian)	142/274	22	73	47	167	117	21	136	117	370	178	0.324	0.029
Feng et al., 2016	China (Asian)	177/236	24	83	70	223	131	28	107	101	309	163	0.345	0.967
Hua et al., 2016	China (Asian)	1142/1173	161	555	426	1407	877	189	551	433	1417	929	0.396	0.537
Li et al., 2016	China (Asian)	216/216	22	106	88	282	150	18	103	95	293	139	0.321	0.174
Lu et al., 2016	China (Asian)	184/206	24	91	69	229	139	22	97	87	271	141	0.342	0.51
Yang et al., 2016	China (Asian)	155/246	33	73	49	171	139	32	111	103	317	175	0.355	0.807
Zhou et al., 2016	China (Asian)	431/432	61	196	174	544	318	46	193	193	579	285	0.329	0.827
rs2094258 C>T			CC	TC	TT	C	T	CC	TC	TT	C	T		
He et al. 2012	China (Asian)	1125/1196	457	518	150	1431	819	457	560	179	1474	918	0.383	0.728
Yang et al., 2012	China (Asian)	337/347	131	149	57	410	264	145	166	36	456	238	0.342	0.252
Chen et al., 2016	China (Asian)	692/771	287	304	101	878	506	291	368	112	950	592	0.383	0.803
Feng et al., 2016	China (Asian)	177/238	15	75	87	52	302	15	96	127	126	350	0.735	0.577
Hua et al., 2016	China (Asian)	1142/1173	499	508	135	1506	778	527	524	122	1578	768	0.327	0.623
Lu et al., 2016	China (Asian)	184/206	17	67	100	101	267	13	72	121	98	314	0.762	0.605
Yang et al., 2016	China (Asian)	155/246	71	74	10	216	94	121	111	14	353	139	0.282	0.076
rs1047768 T>C			TT	CT	CC	T	C	TT	CT	CC	T	C		
Hussain et al., 2009	China (Asian)	170/386	97	61	12	255	85	189	168	29	546	226	0.292	0.173
He et al., 2012	China (Asian)	1125/1196	571	469	85	1611	639	610	474	112	1694	698	0.291	0.155
Li et al., 2014	China (Asian)	217/217	37	95	85	169	265	29	93	95	151	283	0.652	0.414
Hua et al., 2016	China (Asian)	1142/1173	607	445	90	1660	624	625	461	87	1711	635	0.27	0.875
Li et al., 2016	China (Asian)	216/216	57	92	67	206	226	68	87	61	223	209	0.483	0.004
Bai et al., 2016	China (Asian)	194/225	41	98	55	180	208	32	106	87	170	280	0.622	0.975
rs2296147 T>C			TT	CT	CC	T	C	TT	CT	CC	T	C		
Duan et al., 2012	China (Asian)	403/403	257	122	24	636	170	260	132	11	652	154	0.191	0.232
He et al., 2012	China (Asian)	1125/1196	700	371	54	1771	621	742	398	56	1882	510	0.213	0.779
Yang et al., 2012	China (Asian)	337/347	208	105	24	521	173	196	110	41	502	192	0.276	≤0.001
Chen et al., 2016	China (Asian)	692/771	442	217	33	1101	441	475	264	32	1214	328	0.212	0.535
Hua et al., 2016	China (Asian)	1142/1173	725	364	53	1814	532	746	388	39	1880	466	0.198	0.182
rs873601 G>A			GG	AG	AA	G	A	GG	AG	AA	G	A		
He et al., 2012	China (Asian)	1125/1196	274	560	291	1108	1142	327	605	264	1259	1133	0.473	0.616
Yang et al., 2012	China (Asian)	337/346	96	163	78	355	319	91	164	91	346	346	0.5	0.333
Chen et al., 2016	China (Asian)	692/771	172	333	187	677	707	205	396	170	806	736	0.477	0.415
Hua et al., 2016	China (Asian)	1142/1173	311	557	274	1179	1105	323	598	252	1244	1102	0.469	0.424
Zhou et al., 2016	China (Asian)	431/432	115	215	101	445	417	132	200	100	464	400	0.463	0.152

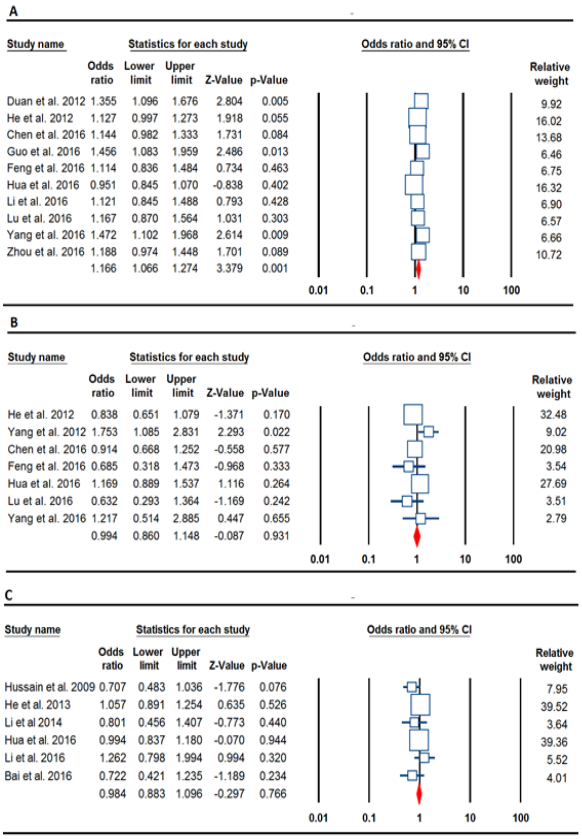

Figure 1. Forest Plots Showed Significant Association between Polymorphisms of Ercc5 Gene and Susceptibility to Gastric Cancer. A: rs751402 C>T (allele model: T vs. C), B: rs2094258 C>T (homozygote model: TT vs. CC), C: rs1047768 T>C (heterozygote model: CT vs. TT). Horizontal lines represented 95% CI, and dotted vertical lines represent the value of the summary OR.

0.868, 95% CI = 0.717-1.051, p = 0.148). In the rs2296147 T>C polymorphism, we observed this polymorphism was significantly associated with gastric cancer risk under allele model (C vs. T: OR = 1.268, 95% C = 1.049-1.532, p= 0.014), but not under the homozygote model (CC vs. TT: OR = 0.786, 95% CI = 0.314-1.967, p = 0.607), the heterozygote model (CT vs. TT: OR = 0.947, 95% CI = 0.859-1.044, p = 0.271), the dominant model (CC+CT vs. TT: OR = 1.665, 95% CI = 0.923-3.004, p = 0.090), and the recessive model (CC vs. CT+ TT: OR = 1.130, 95% CI = 0.782-1.632, p = 0.517). The susceptibility effect on gastric cancer was also observed for the A allele of the rs873601 G>A Polymorphism under the allele model (A vs. G, OR = 1.087, 95% C = 1.021-1.159, p= 0.010), the homozygote model (AA vs. GG, OR = 1.184, 95% CI = 1.043-1.343, p = 0.009), and the recessive model (AA vs. AG+GG, OR = 1.156, 95% CI = 1.040-1.284, p = 0.007), but not under the heterozygote model (AG vs. GG, OR = 1.040, 95% CI = 0.934-1.158, p = 0.478) and the dominant model (AA+AG vs. GG, OR = 1.084, 95% CI = 0.979-1.199, p = 0.121). No significant association was observed between gastric cancer risk and rs2094258 C>T polymorphism (allele model: C vs. T: OR = 1.076, 95% C = 0.926-1.251, p= 0.339; homozygote model: CC vs. TT: OR = 0.994, 95% CI = 0.860-1.148, p = 0.931; heterozygote model: CT vs. TT: OR = 0.948, 95% CI = 0.860-1.046, p = 0.286; the dominant model:

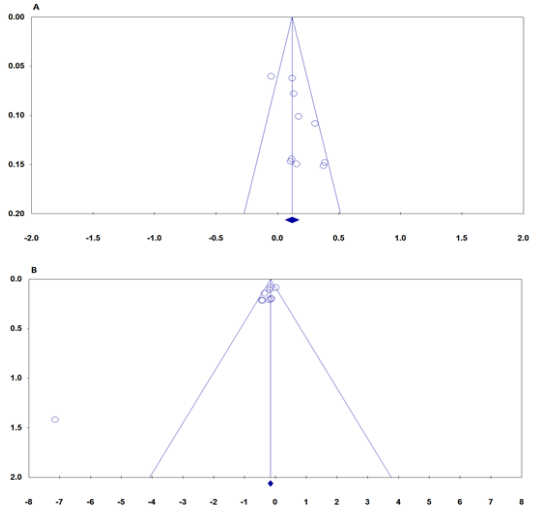

Figure 2. Begg's Funnel Plots of ERCC5 Rs751402 C>T Polymorphism And Gastric Cancer Risk For Publication Bias Test. A: Allele model (T vs. C), and B: Recessive model (TT vs. TC+CC). Each point represents a separate study for the indicated association.

CC+CT vs. TT: OR = 1.031, 95% CI = 0.939-1.132, p = 0.518; recessive model: CC vs. CT+ TT: OR = 1.008, 95% CI = 0.890-1.143, p = 0.896) as well as the rs1047768 T>C polymorphism (allele model: C vs. T: OR = 0.950, 95% C = 0.880-1.025, p= 0.183; homozygote model: CC vs. TT: OR = 0.881, 95% CI = 0.740-1.048, p = 0.152, heterozygote model: CT vs. TT: OR = 0.984, 95% CI = 0.883-1.096, p = 0.766; the dominant model: CC+CT vs. TT: OR = 0.966, 95% CI = 0.872-1.069, p = 0.502; recessive model: CC vs. CT+ TT: OR = 0.881, 95% CI = 0.756-1.027, p = 0.105).

MAFs

The minor allele frequencies (MAFs) in the healthy subjects were calculated from the corresponding genotype distribution (Table 1). Frequencies of the rs751402 C>T, rs2094258 C>T, rs1047768 T>C, rs2296147 T>C and rs873601 G>A alleles were 0.278-0.396, 0.282-0.762, 0.270-0.291, 0.191-0.276, and 0.463-0.500, respectively.

Sensitivity Analysis

We have performed a sensitivity analysis by removing the individual studies sequentially to assess the effect of individual studies. The results detected did not differ from the initial analysis. Moreover, we have performed sensitivity analysis by omitting four studies in which the genotype distributions of ERCC5 gene polymorphisms in the control groups significantly deviated from the HWE ($p<0.005$). However, the significance of pooled ORs not influenced by omitting the studies, indicating that our results was stable and reliable.

Publication Bias

Begg's funnel plot and Egger's test were used to assess the publication bias in the current meta-analysis. The Funnel plots' shape did not reveal obvious evidence of asymmetry. The results of Egger's test statistically confirmed the absence of publication bias for rs2094258

Table 2. The Meta-Analysis of XPG Polymorphisms and Gastric Cancer Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
rs751402 C>T										
	T vs. C	Random	48.16	0.043	1.166	1.066-1.274	3.379	0.001	0.152	0.033
	TT vs. CC	Random	54.15	0.02	0.723	0.587-0.890	-3.053	0.002	0.175	0.032
	TC vs. CC	Random	47.46	0.047	0.868	0.717-1.051	-1.448	0.148	0.152	0.015
	TT+TC vs. CC	Fixed	46.18	0.053	0.853	0.757-0.961	-2.611	0.009	0.107	0.017
	TT vs. TC+CC	Random	72.98	0.001	0.793	0.659-0.955	-2.442	0.015	0.02	0.006
rs2094258 C>T										
	T vs. C	Random	76.21	≤0.001	1.076	0.926-1.251	0.955	0.339	0.229	0.234
	TT vs. CC	Fixed	46.38	0.083	0.994	0.860-1.148	-0.087	0.931	1	0.999
	TC vs. CC	Fixed	0	0.734	0.948	0.860-1.046	-1.066	0.286	0.367	0.604
	TT+TC vs. CC	Fixed	15.45	0.312	1.031	0.939-1.132	0.646	0.518	0.367	0.334
	TT vs. TC+CC	Fixed	40.77	0.119	1.008	0.890-1.143	0.131	0.896	0.548	0.558
rs1047768 T>C										
	C vs. T	Fixed	50.13	0.074	0.95	0.880-1.025	-1.331	0.183	0.452	0.301
	CC vs. TT	Fixed	43.04	0.118	0.881	0.740-1.048	-1.432	0.152	0.707	0.498
	CT vs. TT	Fixed	22.78	0.263	0.984	0.883-1.096	-0.297	0.766	0.707	0.283
	CC+CT vs. TT	Fixed	41.67	0.127	0.966	0.872-1.069	-0.672	0.502	0.452	0.245
	CC vs. CT+TT	Fixed	20.45	0.279	0.881	0.756-1.027	-1.621	0.105	1	0.963
rs2296147 T>C										
	C vs. T	Random	82.83	≤0.001	1.268	1.049-1.532	2.458	0.014	0.462	0.355
	CC vs. TT	Random	93.96	≤0.001	0.786	0.314-1.967	-0.515	0.607	0.806	0.417
	CT vs. TT	Fixed	0	0.945	0.947	0.859-1.044	-1.101	0.271	0.248	0.22
	CC+CT vs. TT	Random	97.1	≤0.001	1.665	0.923-3.004	1.694	0.09	0.22	0.089
	CC vs. CT+TT	Random	64.17	0.025	1.13	0.782-1.632	0.648	0.517	0.806	0.685
rs873601 G>A										
	A vs. G	Fixed	12.26	0.336	1.087	1.021-1.159	2.586	0.01	0.22	0.29
	AA vs. GG	Fixed	12.63	0.333	1.184	1.043-1.343	2.604	0.009	0.462	0.252
	AG vs. GG	Fixed	0	0.663	1.04	0.934-1.158	0.709	0.478	0.806	0.827
	AA+AG vs. GG	Fixed	0	0.578	1.084	0.979-1.199	1.549	0.121	0.806	0.719
	AA vs. AG+GG	Fixed	23.67	0.263	1.156	1.040-1.284	2.685	0.007	0.22	0.126

C>T, rs1047768 T>C, rs2296147 T>C and rs873601 G>A polymorphisms. However, the results of Egger's test statistically showed evidence of publication bias for rs751402 C>T under all five genetic models (T vs. C: P_{Beggs}= 0.152, P_{Eggers} = 0.033; TT vs. CC: P_{Beggs}= 0.175, P_{Eggers} = 0.032; TC vs. CC: P_{Beggs}= 0.152, P_{Eggers} = 0.015; TT+TC vs. CC: P_{Beggs}= 0.107, P_{Eggers} = 0.017; and TT vs. TC+CC: P_{Beggs}= 0.020, P_{Eggers} = 0.006; Table 2, Figure 2).

Discussion

To date, several single nucleotide polymorphisms (SNPs) in ERCC5 gene have been identified, and have been studied for their association with different cancer risk, such as rs751402 C>T, rs2296147 T>C, rs873601 G>A, rs2094258 C>T, rs1047768 T>C, rs17655G>C, rs2018836G>A, and rs3818356G>A (Chen et al., 2016; Guo et al., 2016; Feng et al., 2016). Of these, we have found that five polymorphisms including rs751402 C>T, rs2094258 C>T, rs1047768 T>C, rs2296147 T>C, and rs873601 G>A most frequently investigated for their associations with risk of gastric cancer (Chen et al., 2016; Duan et al., 2015; Feng et al., 2016; Guo et al., 2016; He et al., 2012; Hua et al., 2016; Li et al., 2016; Lu et al., 2016; Yang et al., 2016; Zhou et al., 2016). Interestingly, rs17655G>C (Asp1104His) polymorphism as the most widely studied polymorphism of ERCC5 gene in various cancers not investigated in the gastric cancer.

In the current meta-analysis, a total of 33 case control studies in 15 publications with 16,783 cancer cases and 23,063 controls were selected. When all the studies were pooled together, our results suggested that the ERCC5 gene rs751402 C>T, rs2296147 T>C, and rs873601 G>A polymorphisms are associated with risk of gastric cancer, however, this risk was not observed for the other two SNPs (rs2094258 C>T and rs1047768 T>C). In a most recent meta-analysis based on 47 case-control studies, Huang et al., (2017) showed ERCC5 gene rs873601 G>A polymorphism was significantly associated with an increased risk of different cancers. However, they have found only two rs751402 C>T and rs873601 G>A polymorphisms were significantly associated with an increased risk of gastric cancer. Na et al., (2015) in a case control study reported that rs751402 C>T, rs2296147

T>C, and rs873601 G>A polymorphisms not significantly associated with risk of breast cancer in a Chinese population. In another study, Hua et al., (2016) have found that rs2094258 C>T, rs751402 C>T, and rs873601 G>A polymorphisms were significantly associated with colorectal cancer susceptibility. However, they have identified a protective association between rs751402 C>T and risk of colorectal cancer. Zhu et al., (2012) in a case-control study of 1,115 esophageal squamous cell carcinoma (ESCC) cases found that the rs2296147 T>C polymorphism was associated with ESCC risk; however, they have not observed this risk for rs2094258C>T and rs873601 G>A polymorphism. This result could be interpreted partially on the basis of the different functions of ERCC5 gene (such as RNA polymerase II transcription, and transcription-coupled DNA repair) in different tumor types as a result of distinct mechanisms in terms of cancer susceptibility. On the other hand, it seems this probability may be that different types of cancer may have different mechanism of carcinogenesis (Yazdi et al., 2015).

We have found statistically significant level of heterogeneity predominantly for rs751402 C>T and rs2296147 T>C polymorphisms, which might have distorted the results. Heterogeneity may be due to many factors, such as study characteristics, small sample size, source of controls, genotyping methods and difference in clinical and/or environmental factors (Jia et al., 2017; Jafari-Nedooshan et al., 2017; Kamali et al., 2017; Sobhan et al., 2017). In the current meta-analysis subgroup analysis to better ensure the reliability of our results and identifying source of heterogeneity not explored due lack of original data. However, we suggested that the interaction between two or more polymorphisms might be representing an additional source of heterogeneity in the current meta-analysis.

To the best knowledge this was the first particular meta-analysis conducted to evaluate the association between ERCC5 gene polymorphisms and gastric cancer risk. However, in interpreting results of the current meta-analysis, some limitations should be acknowledged. First, although the sample size of our study was relatively large, the statistical power was still limited only to the Chinese populations, which produced selection bias at the start of the current meta-analysis. Therefore, studies with larger sample sizes in other ethnicities should be undertaken to validate our findings. Second, in the current meta-analysis we have included only articles in English and Chinese language; thus, studies written in other languages were neglected. Third, although we have performed a comprehensive search to identify eligible studies for current meta-analysis, it was still possible that a few studies meeting inclusion criteria were not included, which could to cause publication bias. Third, because of the lack of original data, we did not conduct a more precise analysis based on single-factor estimates without adjustment for age, sex, histological type, environmental factors and other risk factors (e.g. nutritional behavior, smoking, drinking status), which may cause serious confounding bias. Hence, a precise analysis should be performed if the individual data were available. Finally, it is essential to examine the gene-environment and gene-gene interactions at the levels of individual studies and meta-analysis. To achieve this goal, one usually needs to perform a meta-analysis of individual data, which is not always practical for the majority of available meta-analyses. However, our meta-analysis did not evaluate any potential gene-gene interaction and gene-environment interaction due to lack of relevant published data.

In conclusion, our findings provide clear evidence that ERCC5 gene rs751402 C>T, rs2296147 T>C, and rs873601 G>A polymorphisms are associated with the susceptibility of gastric cancer, but not rs2094258 C>T and rs1047768 T>C. Further well-designed studies with larger sample sizes in the different ethnic groups will be necessary to validate the findings in the current meta-analysis.

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