RESEARCH ARTICLE

Associations of *ERCC4* rs1800067 Polymorphism with Cancer Risk: an Updated Meta-analysis

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Abstract

Background: Results from previous studies concerning the association of *ERCC4* rs1800067 polymorphism with risk of cancer were inconsistent. To explore the exact relation with susceptibility, we conducted the present meta-analysis. Materials and Methods: Literature of electronic databases including PubMed, Web of Science, EMBASE, Wanfang and Chinese National Knowledge Infrastructure (CNKI) were systematically searched. ORs and their 95%CIs were used to assess the strength of associations between *ERCC4* polymorphism and cancer risk. Results: There was no significant association between *ERCC4* rs1800067 AA or AG genotypes and overall risk of cancer (AA vs. GG: OR=0.998, 95%CI=0.670-1.486, *P*=0.992; AG vs. GG: OR=0.970, 95%CI=0.888-1.061, *P*=0.508). A dominant genetic model also did not demonstrate significant association of (AA+AG) genotype carriers with altered risk of overall cancer (OR=0.985, 95%CI=0.909-1.068, *P*=0.719). In addition, no significant association was observed between A allele of *ERCC4* rs1800067 A/G polymorphism and altered cancer risk compared with G allele (OR=0.952, 95%CI=0.851-1.063, *P*=0.381). Subgroup analysis suggested that AA genotype carriers were significantly associated with decreased risk of glioma compared with wild-type GG genotype individuals (OR=0.523, 95%CI=0.275-0.993, *P*=0.048). For subgroup of lung cancer, A allele of *ERCC4* rs1800067 A/G polymorphism was significantly associated with decreased risk of lung cancer compared with G allele (OR=0.806, 95%CI=0.697-0.931, *P*=0.003). Conclusions: This meta-analysis indicated that *ERCC4* rs1800067 A/G polymorphism might not be associated with risk of overall cancer. However, individuals with the AA genotype were associated with significantly reduced risk of glioma compared with wild-type GG genotype; The A allele was associated with significantly reduced risk of lung cancer compared with G allele. Future large-scale studies performed in multiple populations are warranted to confirm our results.

Keywords: *ERCC4* - polymorphism - cancer - meta-analysis

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Introduction

DNA repair system play a pivotal role in maintaining normal functions of cells (Lindahl and Wood, 1999). In recent years, emerging numbers of studies investigated the relation of DNA damage and repair with the occurrence of cancer. Humans cells employ multiple and specific repair pathways such as nucleotide excision repair (NER) and base excision repair (BER) to repair DNA damage. NER is a versatile system that monitors and repairs a variety of DNA damage, including UV-induced cyclobutane pyrimidine dimers, bulky adducts and DNA crosslinks (de Laat et al., 1999). Excessive DNA damage may give rise to cancer, therefore NER exert important effect in the initiation and development of cancer.

NER system is composed of multiple steps including damage recognition, damage demarcation and unwinding, damage incision and new strand ligation (Friedberg, 2001). Each step requires corresponding functional proteins, and various factors are involved in this complex and precise process, including ERCC1, ERCC2, ERCC3, *ERCC4*, ERCC5, XPA, XPC, DDB2 and so on. Excision repair cross-complementation group 4 (*ERCC4*), alternatively known as XPF, is an important member of NER system. The XPF-ERCC1 heterodimer is responsible for the 5' incision of the dual incision process in the NER pathway (Fagbemi et al., 2011). Besides, the XPF-ERCC1 heterodimer also exerts an important role in maintaining telomere stability and repairing interstrand cross-links (Niedernhofer et al., 2004).

Studies suggested that *ERCC4* gene possessed hundreds of single nucleotide polymorphisms (SNPs), some of which have been linked to the susceptibilities to bladder cancer, lung cancer, breast cancer, colorectal

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cancer and so on. *ERCC4* rs1800067 A/G polymorphism could cause the change from Arg to Gln, which may lead to the alternation of ERCC4 protein function and thus influencing the role of NER in carcinogenesis. A number of researches have been conducted to explore the association of *ERCC4* rs1800067 A/G polymorphism with susceptibility to cancer. However, the results from individual studies were inconsistent (Huang et al., 2006; Yu et al., 2012; Wang et al., 2013; Steck et al., 2014). Previous meta-analysis did not find significant association of this polymorphism with cancer risk: Ding et al. found *ERCC4* rs1800067 polymorphism was not significantly associated with risk of breast cancer in 2011 (Ding et al., 2011); Shi et al. (2012) did not linked the polymorphism to altered risk of cancer in 2012.

Recently, several studies continued to explore the association of *ERCC4* rs1800067 polymorphism with risk of cancer but the results were controversial (Cheng et al., 2013; Santos et al., 2013; Wang et al., 2013; Wyss et al., 2013; Kohlhase et al., 2014; Steck et al., 2014). Aiming at elucidating the exact relation between *ERCC4* rs1800067 A/G polymorphism with risk of cancer, we perform the current meta-analysis by collecting the data from published case-control studies concerning the role of rs1800067 polymorphism in carcinogenesis.

Materials and Methods

Identification and eligibility of relevant studies

Literatures of electronic databases including PubMed, Web of Science, EMBASE, Wanfang and Chinese National Knowledge Infrastructure (CNKI) were systematically searched using different combinations of the search terms including "*XPF/ERCC4/Xeroderma pigmentosum group F*", "polymorphism/mutation/variant" and "cancer/neoplasm/malignancy". References cited in each eligible literature were further searched manually for potentially available studies. When overlapping data exists, only the largest study was adopted. The author was contacted for specific raw data if the data provided in the publications were not sufficient. The last search date was March 5th, 2014.

Inclusion and exclusion criteria

Studies included in this meta-analysis must meet the inclusion criteria as follows: case-control studies investigating the association between *ERCC4* gene rs1800067 polymorphism and risk of cancer; studies with sufficient raw data for evaluating odds ratios (OR) and their 95% confidence interval (CI); studies published in English or Chinese. The main reasons for exclusion were no relevance; reviews or meta-analysis; duplicate publications; animal experiments; functional investigations; and not for specific polymorphisms.

Data extraction

Two authors (Quan Yuan and Jingwei Liu) independently extracted the data from the eligible studies. The following data was extracted from individual study: first author name, publication year, ethnicity of the population, type of studied cancer, the source of the control group, numbers of cases and controls and genotyping methods of *ERCC4* polymorphism. The conflict was resolved after discussion and consensus was finally reached on all of the extracted information.

Statistical analysis

The statistical analysis was performed by Stata software (Version 11.0; StataCorp, College Station, TX). ORs and their corresponding 95%CI were applied to evaluate the strength of association between *ERCC4* gene rs1800067 polymorphism and cancer risk. *P* value <0.05 was considered as statistically significant. Heterogeneity was assessed by using Q statistic (*P* <0.10 indicates significant heterogeneity between studies) and I-squared (I^2) value (Higgins and Thompson, 2002). A fixed-effects model using Mantel-Haenszel method (Mantel and Haenszel, 1959) was performed to calculate the pooled ORs when heterogeneity between studies was not significant. Otherwise, a random-effects model using DerSimonian and Laird (1986) method was used. Sensitivity analysis was carried out to explore heterogeneity when significant heterogeneity was indicated. Subgroup analyses were performed to explore the effects of ethnicities and cancer type. In addition, publication bias was evaluated by Begg and Mazumdar (1994) test and Egger et al. (1997) test, respectively. *P* value < 0.1 for Begg's and Egger's tests suggests significant publication bias.

Results

Study characteristics

A total of 94 potentially relevant literatures were initially indentified through electronic databases after removing the duplicates. Sixty-four literatures were excluded after reviewing the titles and abstracts. Thirty full-text articles were further assessed for eligibility. Four publications were excluded because of meta-analysis, control group had cancer patients or not published in English. Finally, 26 full-text articles with eligibility were included in this meta-analysis (Smith et al., 2003; Huang et al., 2006; Mechanic et al., 2006; Moreno et al., 2006; Crew et al., 2007; Jorgensen et al., 2007; Chang et al., 2008; Hung et al., 2008; McWilliams et al., 2008; Rajaraman et al., 2008; Abbasi et al., 2009; Han et al., 2009; Joshi et al., 2009; Agalliu et al., 2010; Rajaraman et al., 2010; Doherty et al., 2011; Krupa et al., 2011; Smith et al., 2011; Gil et al., 2012; Yu et al., 2012; Cheng et al., 2013; Santos et al., 2013; Wang et al., 2013; Wyss et al., 2013; Kohlhase et al., 2014; Steck et al., 2014). The flow chart which reflected the details of article selection was presented in Figure 1.

The main characteristics of the studies selected in this meta-analysis were summarized in Table 1. All the included studies were case-control designed published in English. Twenty-six articles including thirty studies (19514 cases and 20777 controls) were eventually included for meta-analysis. The types of cancer studied in relation to *ERCC4* rs1800067 polymorphism covered breast cancer, colorectal cancer, thyroid cancer, head and neck cancer, glioma, laryngeal cancer, lung cancer and pancreatic cancer. The ethnicities of the included studies

Table 1. Characteristics of the Included Studies in this Meta-analysis

Author	Year	Ethnicity	Cancer type	Case			Control			Genotyping method
				AA	AG	GG	AA	AG	GG	
Sandra Kohlhase	2014	Caucasian	Breast cancer	18	403	3277	8	354	2506	Taqman
Susan E. Steck	2014	Caucasian	Colon cancer	1	52	251	7	74	455	MassArray
Susan E. Steck	2014	African American	Colon cancer	1	8	217	0	16	307	MassArray
LUÍS S. SANTOS	2013	Caucasian	Thyroid cancer	2	23	77	4	38	168	Taqman
Annah B. Wyss	2013	Caucasian, African American	Head and Neck cancer	144		778	154		920	Illumina
Hong-Bin Cheng	2013	Asian	Glioma	149	41	17	182	43	11	MassArray
Xue-Feng Wang	2013	Asian	Glioma	265	59	6	609	36	7	MassArray
Hongping Yu	2012	Caucasian	Head and Neck cancer	8	195	837	8	209	829	SNPlex
Justyna Gil	2012	Caucasian	Colorectal cancer	0	14	119	0	15	83	PCR-RFLP
R. Krupa	2011	Caucasian	Larynx cancer	6	26	221	0	29	224	PCR-RFLP
Jennifer A. Doherty	2011	Caucasian	Endometrial cancer	3	107	593	5	89	620	SNPlex, Taqman
Preetha Rajaraman	2010	Caucasian	Glioma etc.	3	89	434	4	62	405	Q-PCR
Ilir Agalliu	2010	Caucasian	Prostate cancer	13	183	1025	5	202	1012	SNPlex
Ilir Agalliu	2010	African American	Prostate cancer	0	8	136	0	3	78	SNPlex
Amit D.Joshi	2009	Caucasian	Colorectal cancer	40		265	47		313	Q-PCR
Jiali Han	2009	Caucasian	Breast cancer	0	38	200	2	69	401	BeadArray
Rashda Abbasi	2009	Caucasian	Laryngeal cancer	1	44	203	3	90	554	Q-PCR
Tasha R.Smith	2008	Caucasian	Breast cancer	7	39	278	1	47	358	MassArray
Tasha R.Smith	2008	African American	Breast cancer	0	2	51	0	2	73	MassArray
Preetha Rajaraman	2008	Caucasian	Breast cancer	124		714	147		922	Q-PCR
Robert R. McWilliams	2008	Caucasian	Pancreatic cancer	0	59	411	4	111	481	SNPstream, Sequencing
Rayjean J. Hung	2008	Caucasian,Asia	Lung cancer	13	306	2201	21	390	2208	Pooled
Jeffrey S. Chang	2008	Latino	Lung cancer	0	16	97	1	31	267	BeadArray
T. J. Jorgensen	2007	Caucasian	Breast cancer	1	37	221	1	43	231	Q-PCR
Katherine D. Crew	2007	Caucasian	Breast cancer	3	156	859	10	167	888	Q-PCR, Sequenom
Victor Moreno	2006	Caucasian	Colorectal cancer	7	71	282	5	61	257	APEX microarray
Leah E.Mechanic	2006	African American	Breast cancer	1	18	738	0	31	642	Q-PCR, Sequencing
Leah E.Mechanic	2006	Caucasian	Breast cancer	12	185	1049	3	150	980	Q-PCR, Sequencing
Wen-Yi Huang	2006	Mixed	Colorectal cancer	1	78	624	7	86	623	Pooled
Tasha R. Smith	2003	Caucasian	Breast cancer	7	29	217	0	32	236	PCR-RFLP

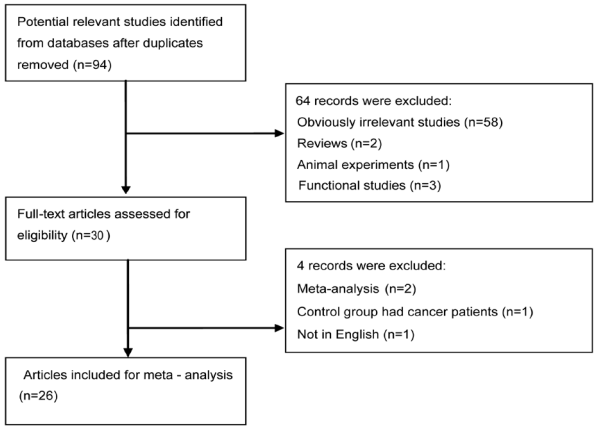

Figure 1. The Flowchart of Literature Inclusion and Exclusion

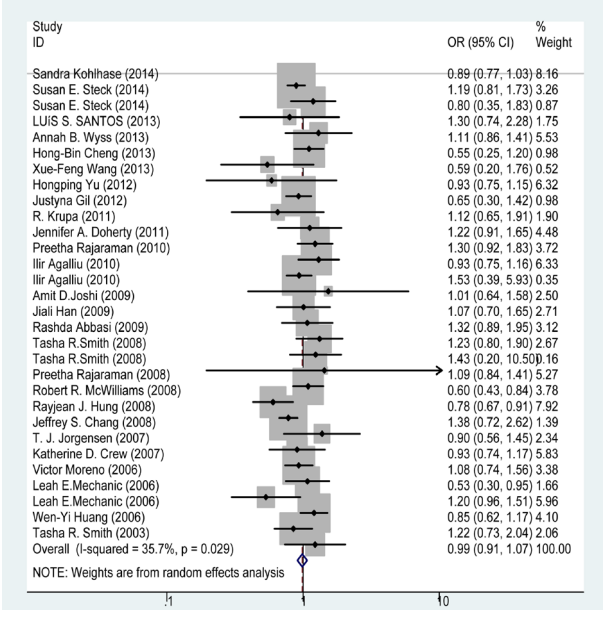

Figure 2. Forest Plot for the Association between *ERCC4* rs1800067 A/G Polymorphism and Cancer Risk ((AA+AG) vs. GG)

had Caucasian, Asian, African American and Latino.

Quantitative data synthesis

Results of the association between *ERCC4* rs1800067 A/G polymorphism and cancer risk was summarized in Table 2. There was no significant association between *ERCC4* rs1800067 AA or AG genotypes and overall risk of cancer (AA vs. GG: OR=0.998, 95%CI=0.670-1.486, *P*=0.992; AG vs. GG: OR=0.970, 95%CI=0.888-1.061, *P*=0.508). Dominant genetic model also did not demonstrate significant association of (AA+AG) genotype carriers with altered risk of overall cancer compared with GG genotype carriers (OR=0.985, 95%CI=0.909-1.068, *P*=0.719, Figure 2). In addition, no significant association was observed between A allele of *ERCC4* rs1800067 A/G polymorphism and altered cancer risk compared with G allele (OR=0.952, 95%CI=0.851-1.063, *P*=0.381, Figure 3).

Subgroup analysis was then performed to explore the effect of different ethnicities and cancer types. For different subgroups of ethnicities, no significant association was found between *ERCC4* rs1800067 A/G polymorphism and altered cancer risk (Table 2).

Table 2. Association between *ERCC4* rs1800067 Polymorphism and Cancer Risk

Genetic model	Group/Subgroup	No.	Heterogeneity Test		Statistical model	Test for overall effect	
			I^2 (%)	P_{het}		OR (95%CI)	*P*
AA vs. GG	Overall	27	39.00%	0.027	R	0.998 (0.670-1.486)	0.992
	Colorectal	4	45.00%	0.141	F	0.606 (0.281-1.308)	0.202
	Breast	8	50.00%	0.051	R	1.853 (0.747-4.596)	0.183
	Lung	2	0.00%	0.817	F	0.632 (0.320-1.246)	0.185
	Glioma	2	0.00%	0.951	F	**0.523 (0.275-0.993)**	**0.048**
	Caucasian	17	37.30%	0.061	R	1.266 (0.777-2.062)	0.344
	African American	2	0.00%	0.834	F	3.321 (0.345-32.018)	0.299
AG vs. GG	Overall	27	35.00%	0.039	R	0.970 (0.888-1.061)	0.508
	Colorectal	5	0.00%	0.444	F	0.995 (0.818-1.211)	0.962
	Breast	9	13.90%	0.318	F	0.946 (0.857-1.045)	0.275
	Lung	2	66.90%	0.082	R	0.970 (0.558-1.687)	0.914
	Glioma	2	56.90%	0.128	F	0.921 (0.464-1.828)	0.813
	Caucasian	18	30.70%	0.106	F	0.983 (0.915-1.056)	0.635
	African American	4	0.00%	0.412	F	0.660 (0.426-1.024)	0.064
(AA+AG) vs. GG	Overall	30	35.70%	0.029	R	0.985 (0.909-1.068)	0.719
	Colorectal	6	0.00%	0.652	F	0.972 (0.815-1.160)	0.753
	Breast	10	25.00%	0.214	F	0.985 (0.899-1.080)	0.752
	Lung	2	64.80%	0.092	R	0.947 (0.557-1.610)	0.841
	Glioma	2	0.00%	0.919	F	0.559 (0.296-1.057)	0.073
	Head and Neck	2	11.20%	0.288	F	1.000 (0.850-1.175)	0.997
	Caucasian	20	26.90%	0.131	F	1.004 (0.939-1.073)	0.908
	African American	4	0.00%	0.439	F	0.701 (0.455-1.079)	0.107
A allele vs. G allele	Overall	27	66.40%	0.000	R	0.952 (0.851-1.063)	0.381
	Colorectal	5	0.00%	0.528	F	0.942 (0.787-1.127)	0.511
	Breast	9	47.70%	0.054	R	1.025 (0.879-1.195)	0.753
	Lung	2	59.40%	0.117	F	**0.806 (0.697-0.931)**	**0.003**
	Glioma	2	88.40%	0.003	R	0.489 (0.228-1.052)	0.067
	Caucasian	17	41.40%	0.034	R	1.039 (0.945-1.141)	0.431
	African American	4	0.00%	0.465	F	0.747 (0.491-1.138)	0.175

*Abbreviations: R, random effect model; F, fixed effect model

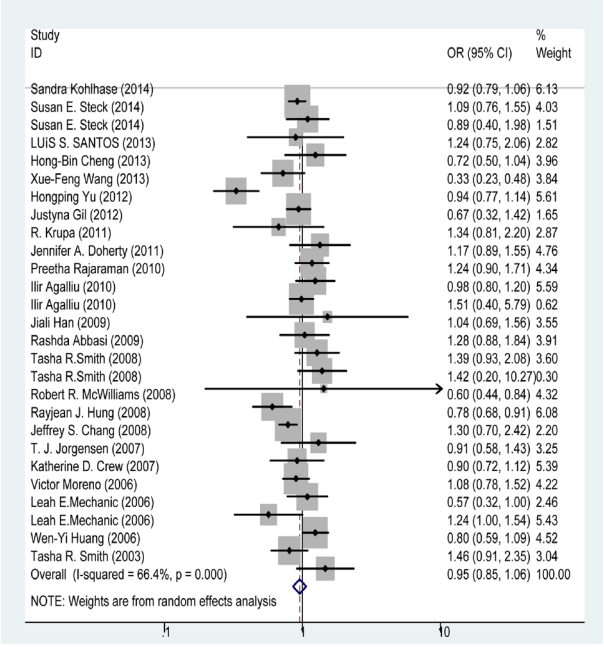

Figure 3. Forest Plot for the Association between *ERCC4* rs1800067 A/G Polymorphism and Cancer Risk (A allele vs. G allele)

For subgroup of glioma, AA genotype carriers were observed to be significantly associated with decreased risk of glioma compared with wild-type GG genotype individuals (OR=0.523, 95%CI=0.275-0.993, *P*=0.048). For subgroup of lung cancer, A allele of *ERCC4* rs1800067 A/G polymorphism was significantly associated with decreased risk of lung cancer compared with G allele (OR=0.806, 95%CI=0.697-0.931, *P*=0.003).

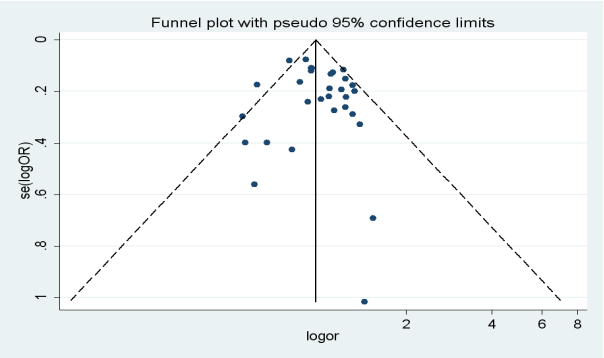

Figure 4. Funnel Plot for Studies of Association between *ERCC4* rs1800067 A/G Polymorphism and Cancer Risk ((AA+AG) vs. GG)

Heterogeneity test, sensitivity analysis and publication bias

In some comparisons of *ERCC4* rs1800067 A/G polymorphism and cancer risk, significant heterogeneities were observed where random effect model was used. Subgroup analysis reduced the heterogeneities in some genetic models (Table 2). We therefore performed sensitivity analysis to detect the influence of individual study on the pooled estimate by omitting one study from the pooled analysis each time. The outcomes suggested that no individual study significantly affected the pooled OR (figure not shown), indicating that the results of the meta-analysis were robust.

The Begg's test and Egger's test were conducted to quantitatively assess the publication bias of the included studies. The detailed information for publication bias test was shown in Table 3. No significant publication bias

Table 3. Publication Bias

Compared genotype	Begg's test		Egger's test	
	z value	P value	t value	P value
AA vs. GG	0.15	0.884	1.30	0.206
AG vs. GG	0.69	0.487	0.80	0.431
(AA+AG) vs. GG	-0.45	0.656	0.89	0.383
A allele vs. G allele	0.15	0.884	0.66	0.517

was observed in the present meta-analysis. Besides, the funnel plot which reflects the studies of the association of (AA+AG) genotype with cancer risk was presented in Figure 4.

Discussion

As a key member of NER system, *ERCC4* polymorphism might be related to cancer susceptibilities. The relation of DNA repair gene polymorphism and cancer risk has been widely studies (Li et al., 2013; Yang et al., 2013). Previous studies concerning the association between *ERCC4* rs1800067 A/G polymorphism and risk of cancer were controversial. By conducting the present meta-analysis, we suggested that *ERCC4* rs1800067 A/G polymorphism might not be associated with risk of overall cancer. However, individuals with AA genotype were associated with significantly reduced risk of glioma compared with wild-type GG genotype; A allele was associated with significantly reduced risk of lung cancer.

Human *ERCC4* gene, also named as XPF, is located at chromosome 6p13.12, consisting of eleven exons and ten introns. *ERCC4* exert its functions in the irreversible dual-incision process during NER by forming an obligate heterodimer complex with ERCC1 and then operating 5' incision to the DNA lesion (Nouspikel, 2009). More importantly, the catalyzing domain that determines NER activity is in *ERCC4* (Enzlin and Scharer, 2002). Additionally, low expression of *ERCC4* has been reported to be related with an elevated risk of head and neck cancer (Wei et al., 2005). Key polymorphism of *ERCC4* might affect the expression and function of *ERCC4* protein and its role in NER system, thus altering individual's susceptibility to cancer. Driven by this hypothesis, an increasing number of studies investigated the association between *ERCC4* rs1800067 A/G polymorphism and risk of cancer in recent years. However, the results from individual studies were inconclusive.

By collecting and analyzing the data from published twenty-six articles including thirty studies conducted on the association of *ERCC4* rs1800067 polymorphism with cancer risk, we found that *ERCC4* rs1800067 AA or AG genotypes was not significantly associated with overall risk of cancer (AA vs. GG: OR=0.998, *P*=0.992; AG vs. GG: OR=0.970, *P*=0.508). Dominant genetic model also did not demonstrate significant association of (AA+AG) genotype carriers with altered risk of overall cancer compared with GG genotype carriers (OR=0.985, *P*=0.719). In addition, no significant association was observed between A allele of *ERCC4* rs1800067 A/G polymorphism and altered cancer risk compared with G allele (OR=0.952, *P*=0.381), indicating that this polymorphism might not be associated with overall risk of cancer. Subgroup analysis found that individuals with AA genotype were associated with significantly reduced risk of glioma compared with wild-type GG genotype; A allele was associated with significantly reduced risk of lung cancer, suggesting that *ERCC4* rs1800067 A/G polymorphism might be involved in the carcinogenesis of glioma and lung cancer. Considering the limited number of studies for certain subgroups, future large-scale investigations are still needed to draw a more reliable conclusion.

Our meta-analysis had advantages than the previously published meta-analysis conducted on the association of *ERCC4* rs1800067 polymorphism and cancer risk. This meta-analysis included all types of cancer into pooled analysis, while the Ding et al. (2011) meta-analysis only investigated breast cancer susceptibility. In addition, Shi et al. (2012) meta-analysis did not find significant association of *ERCC4* rs1800067 polymorphism with risk of overall cancer or in any subgroup. In the present meta-analysis, we included twenty-six articles including thirty studies (19514 cases and 20777 controls) and revealed significant association between *ERCC4* rs1800067 polymorphism and certain cancer subtypes.

Several limitations should also be acknowledged in the present meta-analysis. First, the studied sample was relatively not large for certain subgroup analysis. Second, obvious heterogeneity was observed in the comparisons of *ERCC4* rs1800067 A/G polymorphism and risk of cancer, which could not be fully explained by subgroup analysis. Third, the ethnicities of all the included studies were mainly Caucasians, which may limit the generalizability of our conclusion. Fourth, other important raw data such as age, sex and family history were not available for each individual study so that we could not obtain results with adjustments by other co-variables.

In conclusion, to be concluded, this meta-analysis indicated that *ERCC4* rs1800067 A/G polymorphism might not be associated with risk of overall cancer. However, individuals with AA genotype were associated with significantly reduced risk of glioma compared with wild-type GG genotype; A allele was associated with significantly reduced risk of lung cancer compared with G allele. Future large-scale studies performed in multiple populations are warranted to confirm our results.

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