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ERCC polymorphisms and risk of osteosarcoma: a meta-analysis

X.-J. CHEN, Z.-C. TONG, X. KANG, Z.-C. WANG, G.-L. HUANG, T.-M. YANG, L. DONG

The Department of Bone Diseases, Hong-Hui Hospital, Xi'an Jiaotong University College of Medicine, Xi'an, China

Abstract. – OBJECTIVE: The association between excision repair cross-complementation (ERCC) gene family (ERCC1 and ERCC2) and osteosarcoma risk was controversial. The aim of this study was to evaluate the association between ERCC1 or ERCC2 and osteosarcoma risk by systematic meta-analysis.

MATERIALS AND METHODS: Relative studies were retrieved from electronic databases without language restriction. The last search was updated on March 2017. Quality assessment was analyzed by the Newcastle-Ottawa Scale (NOS) score, which was recommended by the Agency for Healthcare Research and Quality (AHRQ). Meta-analysis was conducted by R language package (R 3.12).

RESULTS: This meta-analysis was performed based on 4 case-control studies that included 1208 cases and 2448 controls. The ERCC2-rs1799793 AA+AC > CC (OR=1.3428, 95% CI=1.0201; 1.7674) had an effect on the risk of osteosarcoma development, whereas, there were no significant associations among the other ERCC SNPs (ERCC1 rs3212986, ERCC1 rs11615, and ERCC2 rs13181) and osteosarcoma.

CONCLUSIONS: The ERCC2 rs1799793 polymorphism is related to the high risk of osteosarcoma development.

Key Words:
Osteosarcoma, Risk, Polymorphism, ERCC1/ERCC2, Meta-analysis.

Introduction

Osteosarcoma, derived from mesenchymal tissues, is usually diagnosed in children and adolescents[1,2]. It usually happened in the distal femur, proximal tibia, and humerus[3]. Traditional treatment for osteosarcoma consists of chemotherapy, chemotherapy as well as surgical resection, or a combination of the above strategies[4]. However, because of late diagnosis and insensitive to chemotherapy or radiotherapy, the survival rate of osteosarcoma patients was poor[5]. Though neoadjuvant chemotherapy with adriamycin, cisplatin, and methotrexate has been reported to be a standard treatment for osteosarcoma with effective clinical outcomes, the response and toxicity to chemotherapeutic drugs are differences among individual patients[6]. Genetic polymorphisms have been proved to be associated with the development of cancer diseases. For instance, rs217727 polymorphism has been confirmed to play an important role in genetic susceptibility to the risk of osteosarcoma, which may improve understanding of the potential contribution of H19 SNPs to cancer pathogenesis[7]. Therefore, it is important to identify more predictive genetic markers related to the osteosarcoma risk.

The nucleotide excision repair (NER) involved in the DNA damage removal pathway plays an important role in cancer progression[8]. In this pathway, the excision repair cross-complementation (ERCC) gene family (ERCC1 and ERCC2) is suggested to regulate the oxidative DNA damage, repair adducts, cross-links and thymidine dimers[9,10]. The single-nucleotide polymorphisms (SNPs) is reported to associated with the deficiency of DNA repair capacity of NER genes, which might result in altered mRNA expression or protein activity[11]. The gene variation of NER pathways has been evaluated as risk factors of osteosarcoma, whereas direct evidence from genetic association studies remains controversial[12,13].

A recent meta-analysis performed by Li et al[6] has showed the association between ERCC1 or ERCC2 and osteosarcoma prognosis. However, the authors of this study did not analyze the ERCC polymorphism with osteosarcoma development/risk. In this research, we performed a meta-analysis from the relevant data to determine the effect of the ERCC1 rs3212986, ERCC1 rs11615, ERCC2

Corresponding Author: Liang Dong, MD; e-mail: liangdongld123@163.com

rs13181 and ERCC2 rs1799793 polymorphisms on osteosarcoma risk.

Materials and Methods

Data Sources

The comprehensive search was performed to retrieve the related studies in Embase (http://www.embase.com), PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Cochrane Library (http://www.cochranelibrary.com/) database with the following key words: "ERCC gene (ERCC2 or ERCC3 or ERCC1 or "excision repair cross-complementing)" in combination with "osteosarcoma" or "osteogenic" or "bone tumor". The last search was updated on March 2017.

Selection Criteria

The included studies should contain the associations between the ERCC gene and osteosarcoma. Meanwhile, the ERCC gene distributions between disease group and control group should be offered. Exclusion criteria were as follows: (1) data were not available for study analysis; (2) non-original studies, such as reviews, letters, comments, etc.; (3) duplicate publication; (4) studies with flawed design.

Data Extraction and Quality Assessment

All the following information was separately extracted by our two investigators, such as the first author's name, publication year, country, genotype data and number of cases and controls in the osteosarcoma group and control group. Quality assessment was analyzed by Newcastle-Ottawa Scale (NOS) score recommended by Agency for Healthcare Research and Quality (AHRQ)[3]. If there were discrepancy between the two investigators, the third investigator was invited to discuss for consensus.

Statistical Analysis

All meta-analysis procedures were performed by the R language package (R 3.12). A chi-square test was used for evaluation of the Hardy-Weinberg equilibrium (HWE) status of the control group[14]. The association between the ERCC2 polymorphism and osteosarcoma risk was analyzed by the pooled odds ratio (OR) and its 95% confidence intervals (CI)[15] based on different gene models. The ERCC related gene models were allele genetic model (wild vs. mutational), additive genetic model (heterozygote vs. wild homozygote), the recessive genetic model (wild homozygote vs. heterozygote + wild homozygote) and dominant genetic model (wild homozygote + heterozygote vs. wild homozygote). The heterogeneity among studies was evaluated by the Q statistics and I^2 test[16]. If there were significant heterogeneities among studies ($p < 0.05$ or $I^2 > 50\%$), the random effect model was used for calculation of pooled OR value. Otherwise, the fixed effect model was used. p-value of less than 0.05 was representative of significant difference.

Results

The Characteristics of the Included Studies

The initial search identified 54 studies (24 from PubMed, 21 from Embase and 9 from Cochrane Library) related to the associations between the ERCC2 polymorphism and osteosarcoma risk. Further screening excluded 13 duplicates and 15 irrelevant studies. The left articles were firstly reviewed the abstract, after which, 2 letters/editorials and 2 case series/case reports were excluded. After full-test evaluation, 7 studies were eliminated because of review (n = 1), duplicated populations (n = 1) and unavailable data (n = 5). Finally, a total of 4 studies[17-20] met the selection criteria were included (Figure 1). The 4 eligible studies published between 2011 and 2016 were distributed in Mexico, Italy and China. Results of quality assessment showed that the NOS scores were ranged from 6 to 7, which were relative high, indicating the relative high qualities of these studies. The ERCC2 related genes included in this study were ERCC1 rs3212986, ERCC1 rs11615, ERCC2 rs13181and ERCC2 rs1799793. Almost all the genetic distributions of these ERCC2 related gene variants were in accordance with HWE (Table I).

Mean Results of Meta-Analysis

ERCC1- rs11615

The between-study heterogeneity was not significant in all the gene models ($p > 0.05$) except the comparison between CC+CT *vs.* TT ($p = 0.0217$). Therefore, the random effect model was used to calculate the pooled OR (95% CI) when comparing CC+CT with TT. The other gene models were evaluated by fixed effect model. As a result, no significant association was identified in the five genetic models, indicating that the

Table I. Characteristics of included studies and the distribution of related genes

Author	Public year	Study location	Study Year	NOS scores	SNP	Wild type	Osteosarcoma				Control				χ^{2*}	*p*
							N	WH	HT	MH	N	WH	HT	MH		
Biason et al[19]	2011	Italy	NA	6	ERCC1 rs3212986	C	124	72	44	8	250	129	98	23	0.482	0.4876
					ERCC1 rs11615	T	126	37	59	30	250	86	111	53	2.315	0.1281
Gómez-Díaz et al[20]	2014	Mexico	2012.5 -2013.12	7	ERCC1 rs11615	T	28	16	9	3	97	59	32	6	0.332	0.5645
					ERCC2 rs13181	A	28	21	7	0	97	64	31	2	0.691	0.4059
					ERCC2 rs1799793	C	28	21	3	4	97	68	8	21	57.830	<0.0001
Jin et al[17]	2015	China	2012.1 -2014.1	6	ERCC1 rs11615	T	148	63	85	198	135	63	-	>0.05		
					ERCC1 rs3212986	C	148	79	69	298	169	129	-	>0.05		
					ERCC2 rs1799793a	C	91	58	33	184	127	57	-	>0.05		
					ERCC2 rs1799793b	C	57	26	31	115	77	38	-	>0.05		
					ERCC2 rs13181	A	148	86	62	298	181	117	-	>0.05		
Ma et al[18]	2016	China	2012.1 -2013.12	6	ERCC2 rs13181	T	141	96	32	13	282	206	58	18	15.942	0.0001
					ERCC2 rs1799793	C	141	60	62	19	282	134	117	31	0.505	0.4775

SNP: Single nucleotide polymorphism; *: Likelihood-ratio, χ^2. WH: Wild homozygote; HT: Heterozygote; MH: Mutational homozygote; NOS: Newcastle-Ottawa Scale; N: The total number of subjects. a: male; b: female.

ERCC1 rs11615 polymorphism was not associated with risk of osteosarcoma (Table II and Figure 2).

ERCC1- rs3212986

Only one study[19] referred to the effect of ERCC1-rs3212986 polymorphism on osteosarcoma risk based on the allele genetic model, additive genetic model and the recessive genetic model. Therefore, we did not perform the pairwise heterogeneity analysis. As for dominant model (AA+AC *vs.* CC), two investigations[17,19] referred its effect on osteosarcoma. No significant heterogeneity was found; thereby the fixed effect model was used to evaluate the pooled effect. Results of meta-analysis showed that there were no significant associations between ERCC1-rs3212986 polymorphism and osteosarcoma risk based on all these models (Table II and Figure 3).

ERCC2- rs13181

The pooled OR was 1.0317 (95% CI=0.5458 - 1.9498), 1.0493 (95% CI = 0.6775 - 1.6254), 1.4508 (95% CI = 0.7022 - 2.9972), 1.4131 (95% CI = 0.6891 - 2.8976), 1.1170 (95% CI = 0.8423 - 1.4813) respectively. Moreover, no significant association was found between ERCC2-rs13181 polymorphism and osteosarcoma risk based on these models (Table II and Figure 4).

ERCC2-rs1799793

The between-study heterogeneity was not significant in all the models ($p > 0.05$); therefore, the fixed-effect model was used for this meta-analysis. A significant association was found comparing AA+AC with CC (OR = 1.3428, 95% CI = 1.0201 - 1.7674). No significant differences were found in other genetic models (Table II and Figure 5).

Discussion

Osteosarcoma is usually occurred in children and young adults, which accounts for about 20% of all primary sarcomas in bone tumor[21]. It was reported that both the ERCC1 and ERCC2 are two key rate rate-limiting enzymes in NER process. ERCC1, in combination with xeroderma pigmentosum complementation group F (XPF) protein family, is related to DNA lesion recognition, while ERCC2, as a subunit of human transcriptional initiation factor, which regulated the activity of ATP-dependent helicase[22]. BRCA1 expression has been confirmed to be negatively correlated with Beclin1 and p62 expression, and implicated in the

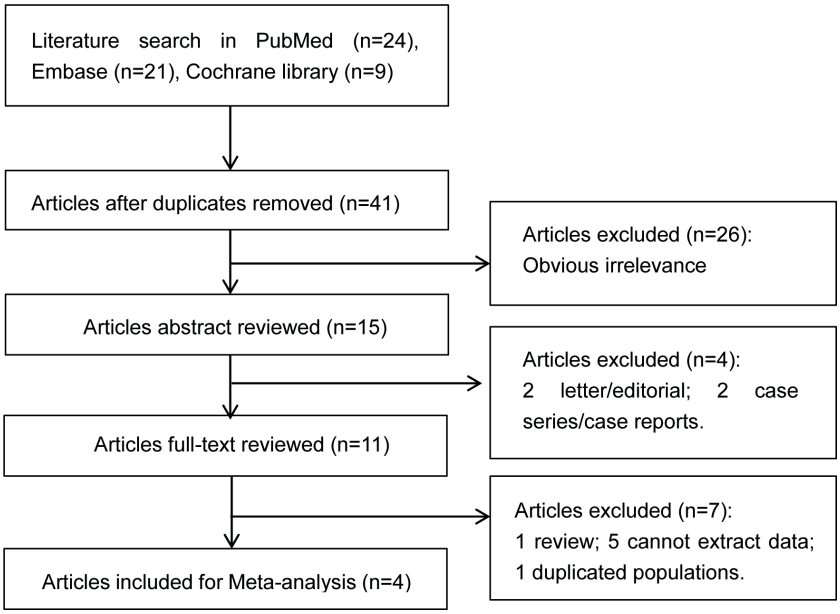

Figure 1. Literature search and study selection.

development of ovarian cancer[23]. Therefore, the SNPs of both ERCC1 and ERCC2 may contribute to the disease susceptibility. In this study, we performed this meta-analysis to evaluate the association between ERCC2 and osteosarcoma, results showed that the ERCC2-rs1799793 AA+AC > CC (OR=1.3428, 95% CI=1.0201; 1.7674) had an effect on the risk of osteosarcoma development, whereas, there are no significant associations between the other ERCC2 SNPs and osteosarcoma.

Misrepaired or unrepaired DNA caused by environmental factors or endogenous factors will result in gene mutations, genomic instability and chromosomal alterations. DNA repair system plays an important role in protection against these mutations. Previous studies[24] reported that patients with several cancers have decreased DNA repair proficiencies. Among DNA repair pathways, NER is an important one that repairs various DNA damage, such as crosslinks, base excision repair, etc.[25]. As the component of NER, ERCC2 involved in nucleotide excision repair and basal transcription[26]. ERCC2 rs1799793, sited in codon 312 is a non-synonymous variant, and is capable to change coding amino acids (Lys751Gln)[27]. Previous works[28] have shown that the Lys751Gln is associated with risk of several cancers, such as bladder cancer, pancreatic cancer[29], and breast cancer[30]. A recent meta-analysis including 5 studies published before April, 2014 also showed a significant association between Lys751Gln polymorphism in the ERCC2 gene and overall survival of osteosarcoma (GG *vs.* AA, Hazard ratios = 0.40; 95 % CI 0.18-0.86)[6]. In this study, we suggested that the Lys751Gln polymorphism might be associated with the risk of osteosarcoma, with OR of 1.3428-fold (95% CI = 1.0201-1.7674) *vs.* to non-cancer control participants. However, the other ERCC2 and ERCC1 polymorphisms did not show any association to osteosarcoma development. The potential heterogeneity should be pointed out in interpretation of this meta-analysis. For ERCC1-rs11615 and ERCC2-rs13181 polymorphism, heterogeneity was found in CC+CT *vs.* TT model and C *vs.* A model, respectively. The gender, age as well as different patient population might attribute to this polymorphism. We should perform subgroup analysis to reduce the effect of these confounding factors to the results of this study; however, only three and two studies included in these two meta-analysis respectively, which was inappropriate to perform stratification analysis. There are several limitations should be considered to interpret the current results. Firstly, as pointed in the above paragraph, we did not perform subgroup analysis because of the limited data. Secondlt, we did not evaluate the publication bias because there were only 4 studies included in this meta-analysis. Thirdlt, there were several studies that did not match the HWE, indicating the poor representativeness of control

Table II. Meta-analysis of ERCC polymorphisms with osteosarcoma risk.

		Sample size		Test of association		Test of heterogeneity[a,b]		
Gene	Gene model	Cases	Control	OR (95%CI)	Model	Q	*p*-value	I^2 (%)
ERCC1- rs11615	C vs. T	308	694	1.1796 [0.8935; 1.5572]	Fixed	0.03	0.8609	0
	CC vs. TT	86	204	1.3723 [0.7913; 2.3798]	Fixed	0.17	0.6801	0
	CC vs. TT+CT	154	347	1.2152 [0.7505; 1.9675]	Fixed	0.33	0.5679	0
	CC+CT vs. TT	302	545	1.6919 [0.9028; 3.1705]	Random	7.66	0.0217	73.6
	CT vs. TT	121	288	1.1880 [0.7670; 1.8400]	Fixed	0.11	0.7437	0
ERCC1- rs3212986	A vs. C	248	500	0.7890 [0.5565; 1.1187]	-	-	-	-
	AA vs. CC	80	152	0.6232 [0.2651; 1.4648]	-	-	-	-
	AA vs. CC+AC	124	250	0.6807 [0.2953; 1.5688]	-	-	-	-
	AA+AC vs. CC	272	548	0.9553 [0.7134; 1.2792]	Fixed	1.74	0.1866	42.7
	AC vs. CC	116	227	0.8044 [0.5089; 1.2715]	-	-	-	-
ERCC2- rs13181	C vs. A	338	758	1.0317 [0.5458; 1.9498]	Random	2.06	0.1517	51.3
	CA vs. AA	156	359	1.0493 [0.6775; 1.6254]	Fixed	0.98	0.3234	0
	CC vs. AA	130	290	1.4508 [0.7022; 2.9972]	Fixed	0.35	0.5563	0
	CC vs. AA+CA	169	379	1.4131 [0.6891; 2.8976]	Fixed	0.25	0.6193	0
	CC+CA vs. AA	317	677	1.1170 [0.8423; 1.4813]	Fixed	1.59	0.4510	0
	A vs. C	338	758	1.0913 [0.8269; 1.4401]	Fixed	1.64	0.2004	39
	AA vs. CC	104	254	1.1157 [0.6379; 1.9513]	Fixed	1.36	0.2436	26.4
ERCC2-rs1799793	AA vs. CC+AC	169	379	1.0565 [0.6189; 1.8036]	Fixed	1.21	0.2706	17.6
	AA+AC vs. CC	317	678	1.3428 [1.0201; 1.7674]	Fixed	4.61	0.2029	34.9
	AC vs. CC	146	327	1.1860 [0.7839; 1.7945]	Fixed	0	0.9728	0

[a]Random-effects model was used when the *p* for heterogeneity test<0.05, otherwise the fixed-effect model was used. [b]$p < 0.05$ is considered statistically significant for Q statis¬tics; OR: Odds ratio; CI: confidence interval.

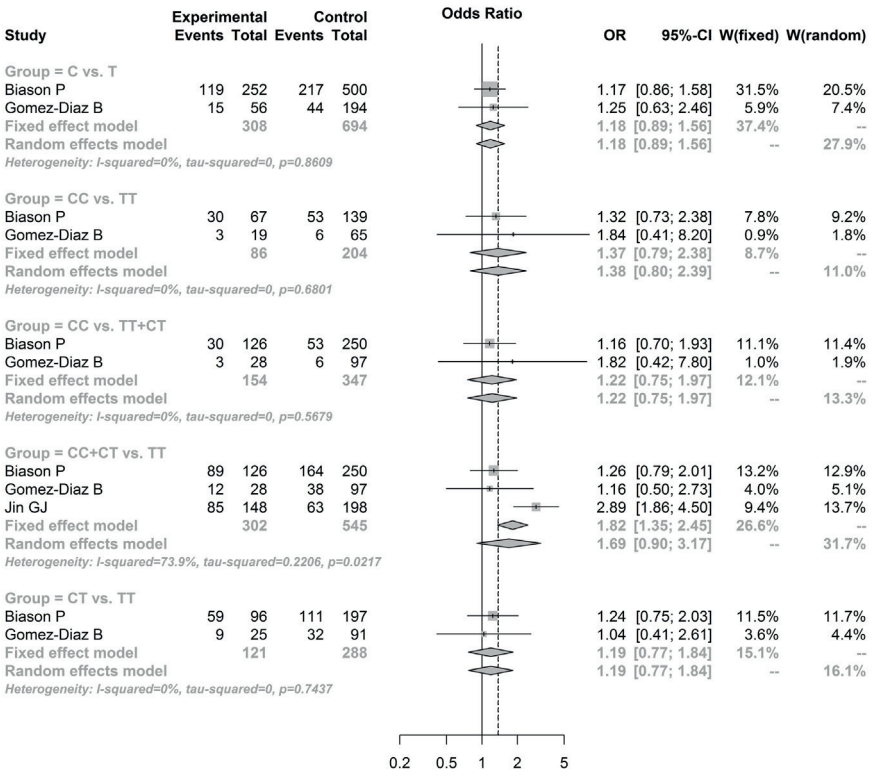

Figure 2. Forest plot of meta-analysis on ERCC1- rs11615.

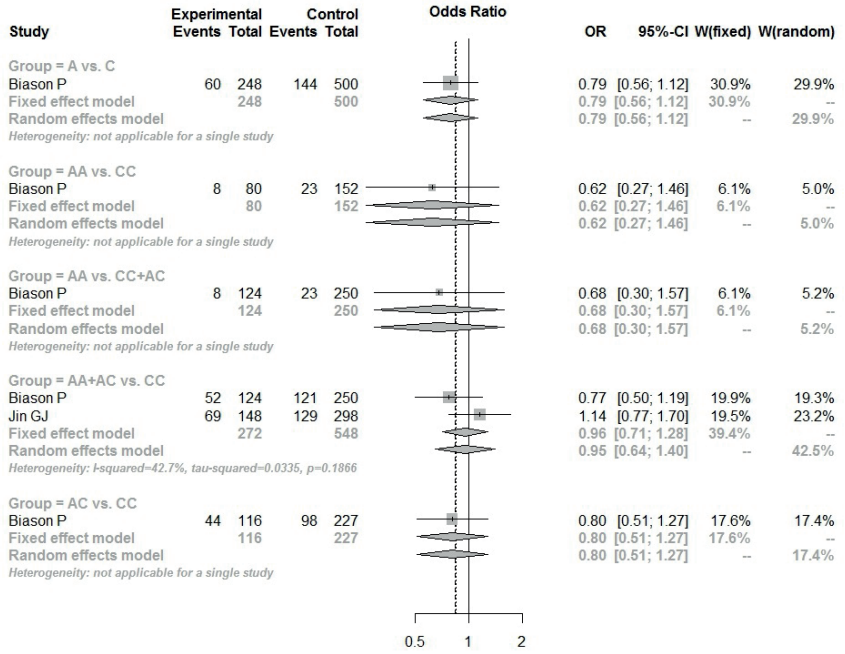

Figure 3. Forest plot of meta-analysis on ERCC1- rs3212986.

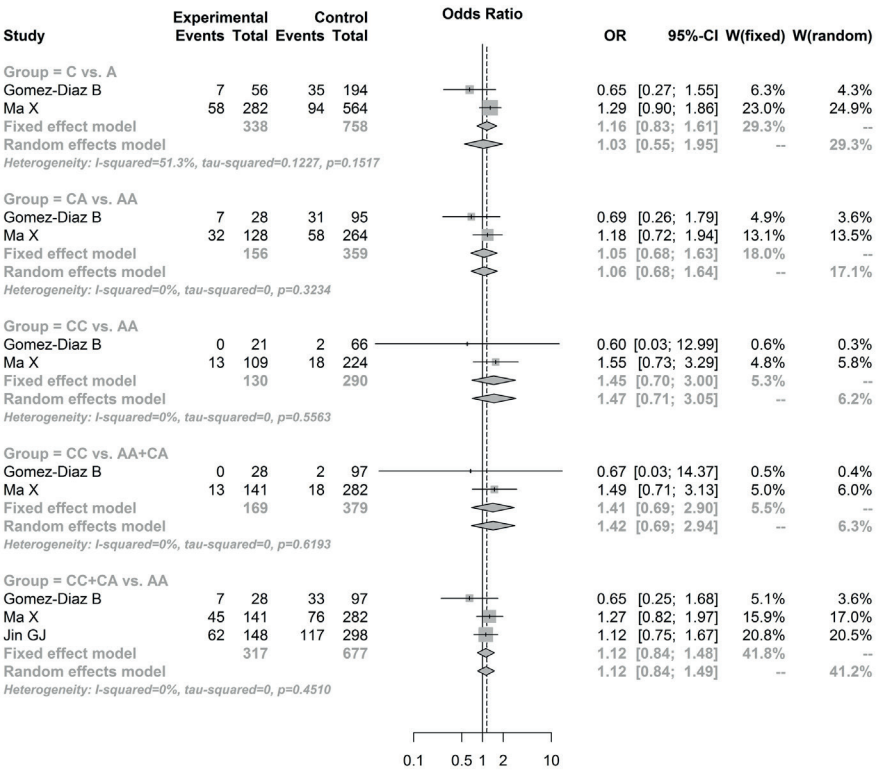

Figure 4. Forest plot of meta-analysis on ERCC2- rs13181.

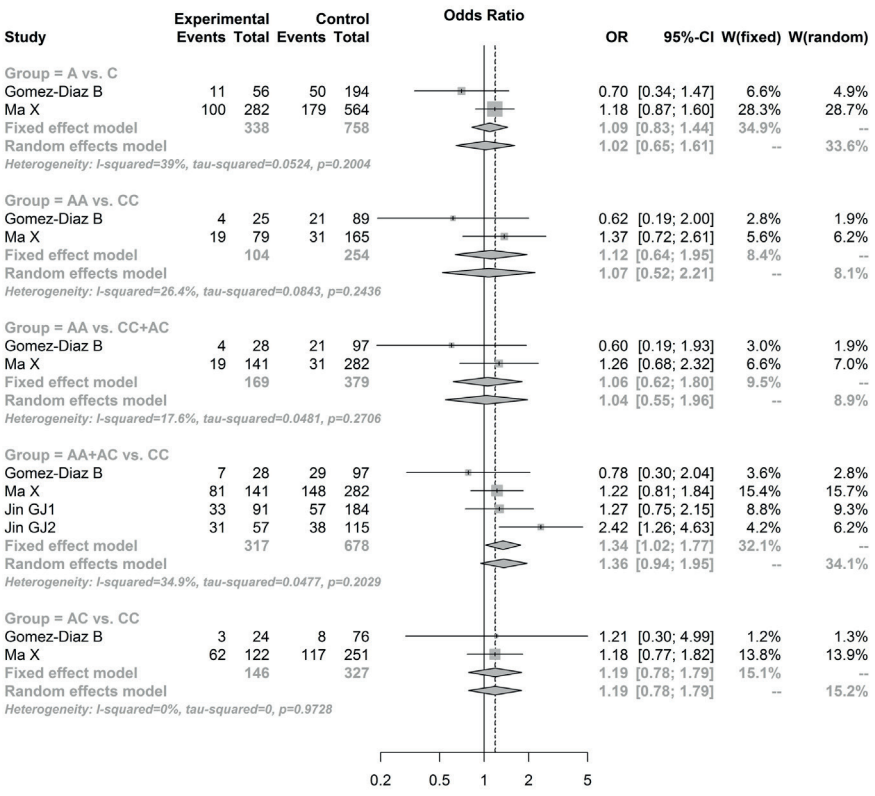

Figure 5. Forest plot of meta-analysis on ERCC2-rs1799793.

samples. However, to our knowledge, this is the first systematic review of the literature by the meta-analysis to explore the association between ERCC1 or ERCC2 polymorphisms and osteosarcoma risk/development. However, more future well-designed studies with large patient number are necessary to further evaluate the relationship between them.

Conclusions

We showed that the rs1799793 polymorphism is related to the high risk of osteosarcoma development, which may improve understanding of the potential contribution of ERCC2 SNPs to cancer pathogenesis.

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