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Original Article

Association of *KRAS* rs712 polymorphism and cancer risk in Chinese population: a meta-analysis

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Abstract: Recently, some studies concerning let-7 binding site polymorphism in *KRAS* 3'-untranslated region (3'-UTR) found that rs712 G/T polymorphism increased cancer risk in Chinese population. However, in consistent or contradictory results occurred. Therefore, we performed a comprehensive meta-analysis to clarify this association. Available data from PUBMED, EMBASE, and Chinese National Knowledge In frastructure (CNKI) databases were retrieved up to Feb 1, 2016. 11 studies including 2906 cases and 3544 controls were included in this meta-analysis. Pooled association was presented as odd ratios (ORs) and 95% confidence intervals (CIs) using a fixed-effect model. Significant associations were found between rs712 polymophism and cancer risk in allelic (T vs G, pooled OR = 1.33, 95% CI = 1.22-1.45, P < 0.001), dominant (TT + GT vs GG, pooled OR = 1.29, 95% CI = 1.17-1.44, P < 0.001), recessive (TT vs GT + GG, pooled OR = 2.05, 95% CI = 1.62-2.59, P < 0.001), and additive model (TT vs GG, pooled OR = 2.71, 95% CI = 1.71-2.75, P < 0.001). No publication bias was detected by Begg and Egger tests. In summary, *KRAS* rs712 polymorphism might confer susceptibility to cancer in Chinese population.

Keywords: KRAS, rs712, polymorphism, cancer, meta-analysis

Introduction

Cancer is the most frequent cause of death in China and becomes a major public health problem, due to its increasing incidence and mortality. In 2015, 4292,000 new cancer cases and 2814,000 cancer deaths were estimated to occur in China, and lung, stomach, esophageal, and liver cancers were identified as leading causes of cancer death [1]. Cancer is a multistep and multifactorial complex process, combined with genetic susceptibility and gene-environment interactions [2, 3]. Genetic variations in some oncogenes which may modify host's susceptibility to cancer, and identification of potential genetic markers will be of great help for screen, diagnosis and prediction of cancer occurrence [4, 5].

KRAS gene, located on12p12.1 chromosome, is an essential oncogene belonging to the *Ras* gene family. It encodes GTPase Kras which performs important function in normal cell proliferation and differentiation involving the RAF/MEK/MAPK, AKT and ERK pathways, and mutation of *KRAS* gene play essential roles in the development of many cancers [6]. Moreover, accumulating evidence shows that repression of *KRAS* expression by microRNA (miRNA) could inhibit tumor growth and invasion [7-9]. Polymorphisms in miRNA complementary in*KRAS* 3'-untranslated region (3'-UTR) may modulate the binding ability of miRNA, and have been found to affect cancer risk and survival [10-13]. Recently, some studies foundlet-7 binding site polymorphism rs712 in *KRAS*3'-UTR was associated with susceptibility of several cancers in Chinese population [14-18], while others got contravisial results [19-22]. Therefore, we performed a comprehensive meta-analysis to clarify this association between *KRAS* rs712 polymorphism and cancer risk in Chinese population.

Methods

Search strategy

Electronic searches were performed in PubMed, Embase, and Chinese National Knowledge

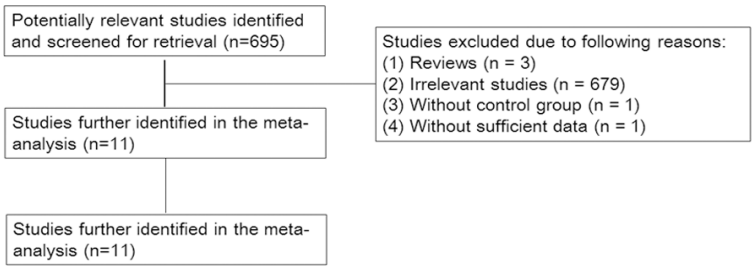

Figure 1. Flow diagram of literature search and selection.

Table 1. Characteristics of 11 studies included in this meta-analysis

Author	Year	Source of Controls	Cancer Type	Mean Age		Sample Size	
				Case	Control	Case	Control
Huang X	2015	HB	BC	50.4	48.3	228	251
Xiong D	2015	PB	HCC	53.3	43.4	262	252
Dai Q	2015	HB	CRC	53.4	55.8	430	430
Jiang QH	2015	HB	CRC	56.2	56.8	586	476
Ni SS	2015	HB	CC	44.1	43.2	204	218
Jin H	2014	HB	PTC	44.8	43.2	252	290
Pan XM	2014	HB	NPC	45.5	44.6	188	356
Pan XM	2014	HB	CRC	59.9	56.8	339	313
Li ZH	2013	HB	GC	57.7	55.8	181	674
Yan L	2013	HB	Glioma	44.4	43.9	153	204
Peng XB	2010	HB	NSCLC	63.2	60.5	83	80

Note: HB, Hospital based; PB, Population based; BC, Breast Cancer; HCC, Hepatocellular Cancer; CRC, Colorectal Cancer; CC, Cervical Cancer; PTC, Papillary Thyroid Cancer; NPC, Nasopharyngeal Cancer; GC, Gastric Cancer; NSCLC, Nonsmall-cell Lung Cancer.

Table 2. Genotype frequencies of rs712 in 11 studies included in this meta-analysis

Author	Case			Control			MAF		HWE
	TT	GT	GG	TT	GT	GG	Case	Control	
Huang X	8	65	155	7	71	173	0.18	0.17	0.93
Xiong D	20	92	150	11	79	162	0.25	0.2	0.73
Dai Q	32	145	253	17	130	283	0.24	0.19	0.67
Jiang QH	38	176	372	12	133	331	0.22	0.16	0.75
Ni SS	19	73	112	6	67	145	0.27	0.18	0.6
Jin H	14	84	154	15	92	183	0.22	0.21	0.44
Pan XM	12	64	112	17	138	201	0.23	0.24	0.27
Pan XM	26	125	188	10	100	203	0.26	0.19	0.58
Li ZH	16	60	105	21	211	442	0.25	0.19	0.49
Yan L	14	56	83	6	61	137	0.27	0.18	0.8
Peng XB	3	31	49	4	25	51	0.22	0.21	0.68

Infrastructure (CNKI) databases to Feb 1, 2016. The following keywords were used: '*KRAS*', 'polymorphism OR variant OR SNP', and 'Cancer OR Tumor OR Carcinoma'. The title and abstract were scanned. In addition, the reference of retrieved articles were reviewed for further identify additional eligible literatures.

Inclusion criteria

The following criteria were used to select eligiblestudies for the current meta-analysis: (1) case-control designed study; (2) association between *KRAS* rs712 polymorphism and cancer risk; (3) available phenotype or allele frequencies; (4) Chinese population. Review, republished or duplicate studies, and studies without available data for odds ratios (OR) and 95% confidence intervals (CI) calculation were excluded.

Data extraction

Articles were reviewed independently by two reviewers (Xiong Wang and Yanjun Lu) and discrepancy was discussed. The following information was collected: first author, publication year, source of control, sample size, cancer type, mean age, and phenotype distribution.

Statistical analysis

We performed the present meta-analysis utilizing STATA software, version 11.0 (STATA Corp., College Station, TX, USA). The Hardy-Weinberg equilibrium (HWE) among the control subjects was assessed, and $P < 0.05$ indicated a significant deviation from equilibrium. Q test and I^2 test were used to examine the heterogeneity. Pooled OR was used to calculate the association stren-

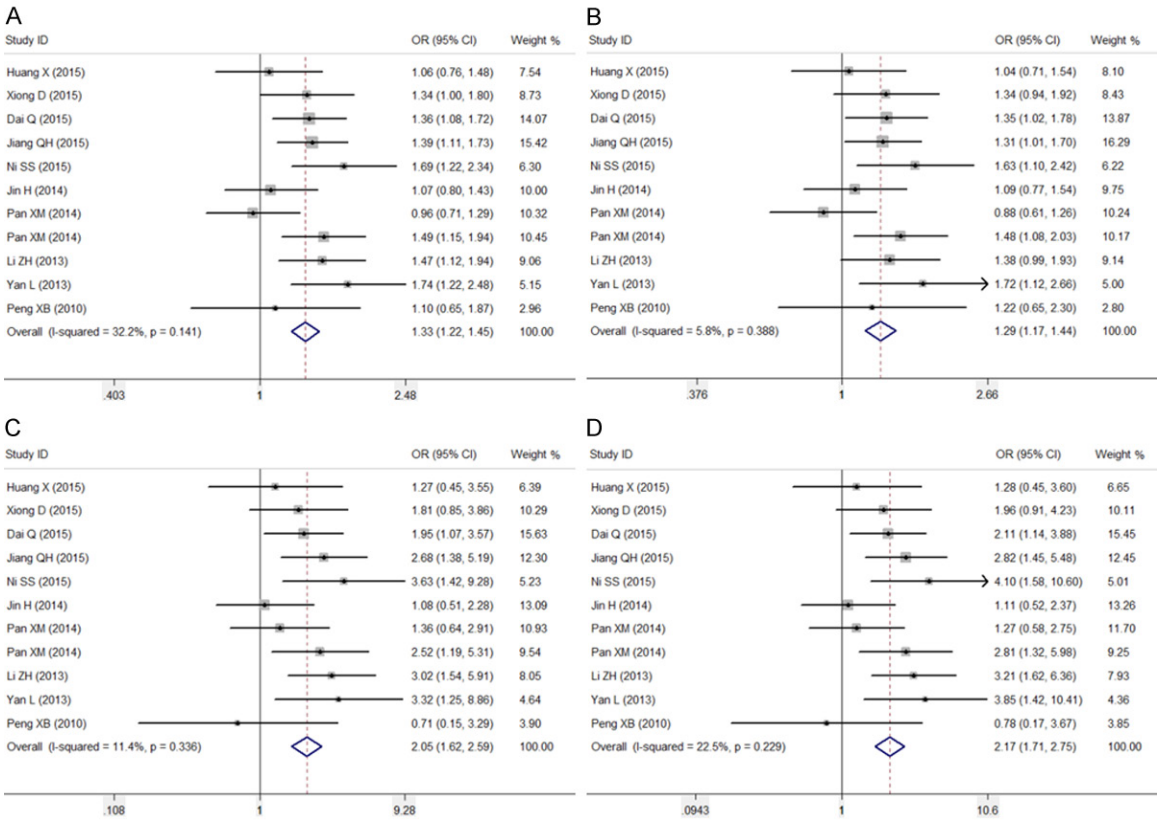

Figure 2. Forest plots for meta-analysis of rs712 polymorphism and Cancer risk in Chinese population. A. Allelic model (T vs G). B. Dominant genetic model (TT + GT vs GG). C. Recessive genetic model (TT vs GT + GG). D. Addictive genetic model (TT vs GG).

Table 3. Meta-analysis of rs712 polymorphism and Cancer risk in Chinese population

Genetic model	P_Q	I^2	OR*	95% CI	P_Z
T vs G	0.14	32.2%	1.33	1.22-1.45	0.000
TT + GT vs GG	0.39	5.8%	1.29	1.17-1.44	0.000
TT vs GT + GG	0.34	11.4%	2.05	1.62-2.59	0.000
TT vs GG	0.23	22.5%	2.17	1.71-2.75	0.000

*Fixed model was used.

gth infour genetic models, including the allelic (T vs. G), dominant (TT + GT vs GG), recessive (TT vs GT + GG), and additive (TT vs GG). Fixed-effect model was applied to merge the ORin the present study. Sensitivity analysis determines the stability of the result. The Egger's test and Begg's test were used to examine publication bias.

Results

Study selection and characteristics

After a comprehensive search, 695 relevant articles were retrieved. After screen of title and abstract, 684 articles wre excluded, of which 3 reviews [23-25], 1 study without control group [11], and 1 study without available genotype information [26]. Overall, 11 relevant studies involving 2906 cases and 3544 controls were included in this meta-analysis [14, 16-22, 27-29]. The selection process was shown in **Figure 1**. The main characteristics of the included 11 studies were shown in **Table 1**. Genotype and allele distribution were shown in **Table 2**. Genotype distribution in the controls of all included studies was consistent with HWE.

Meta-analysis results

Meta-analysis results (**Figure 2**; **Table 3**) showed significant association between *KRAS* rs712 polymorphism and the risk of cancer in allelic model (T vs G, pooled OR = 1.33, 95% CI = 1.22-1.45, P < 0.001); dominantmodel (TT + GT vs GG, pooled OR = 1.29, 95% CI = 1.17-1.44, P

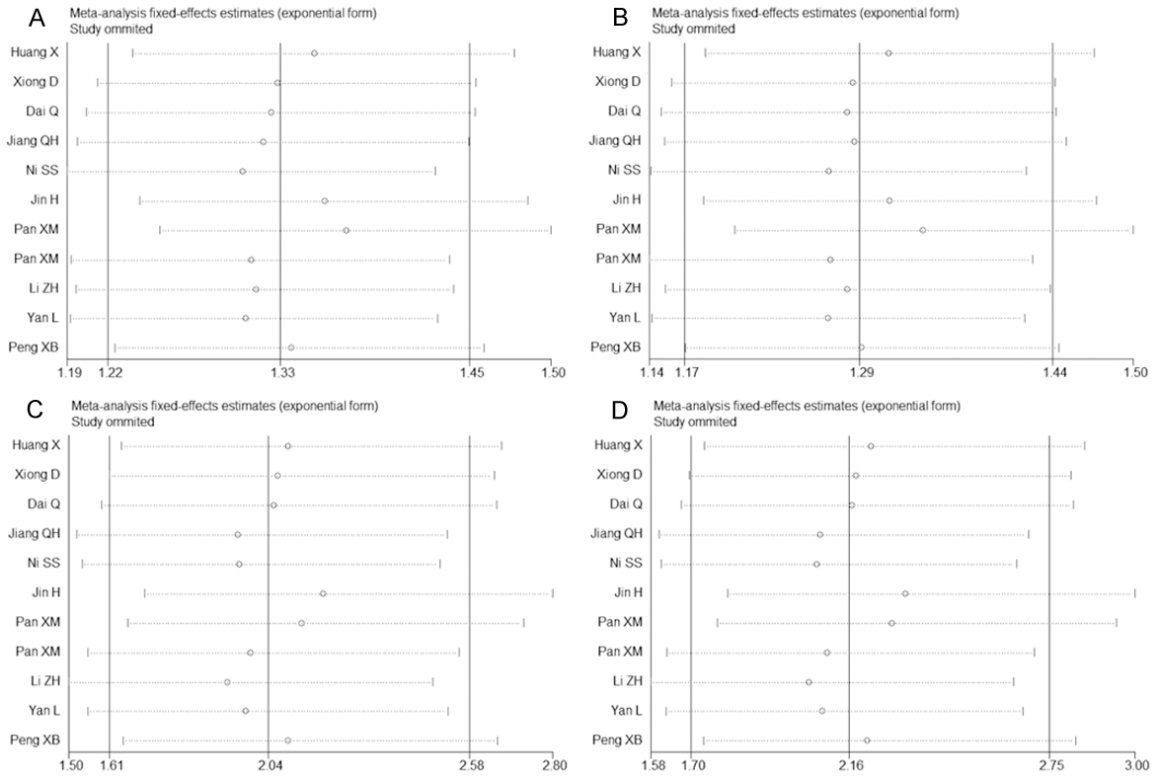

Figure 3. Sensitivity analysis for meta-analysis of rs712 polymorphism and Cancer risk in Chinese population. A. Allelic model (T vs G). B. Dominant genetic model (TT + GT vs GG). C. Recessive genetic model (TT vs GT + GG). D. Addictive genetic model (TT vs GG).

< 0.001); recessive model (TT vs GT + GG, pooled OR = 2.05, 95% CI = 1.62-2.59, P < 0.001); and additive model (TT vs GG, pooled OR = 2.71, 95% CI = 1.71-2.75, P < 0.001). These results suggest that *KRAS* rs712 polymorphism was associated with an increased risk of cancer in all four genetic models.

Sensitivity analysis

Sensitivity analysis were conducted to determine the stability of our findings. A single study was deleted each time to reflect its influence on the pooled ORs, and statistically similar results were obtained (**Figure 3**), indicating that our results were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were carried out to evaluate the publication bias (**Figure 4**; **Table 4**). The shape of the Begg's funnel plots did not show any obvious asymmetry in the overall meta-analysis in all four genetic models. Egger's test did not provide any obvious evidence of publication bias either (T vs G, P = 0.66; TT + GT vs GG, P = 0.92; TT vs GT + GG, P = 0.40; TT vs GG, P = 0.46). The results indicated that no significant publication bias exites in the current meta-analyses.

Discussion

MiRNAs are short non-coding RNA (~22 nucleotides) which post-transcriptionally regulate the gene expression by binding to the 3'-UTR of their target genes. The expression profiles of miRNAs may change during the development of cancer, and a number of miRNAs participate in the development of several cancers via down-regulating oncogenes or tumor supressors [30, 31]. Accumulating evidence shows that variation in the binding site of miRNA in 3'-UTR of target gene mRNA may affect the binding efficiency of the regulatory miRNA, therefore disrupt the inhibitory effect of miRNA on target gene expression positively or negatively [32-34]. Polymorphisms within miRNA binding sites contribute to the susceptibility or prognosis of several cancers [35-37].

Let-7 is a tumor suppressive miRNA family via targeting lots of genes including *KRAS*, and act

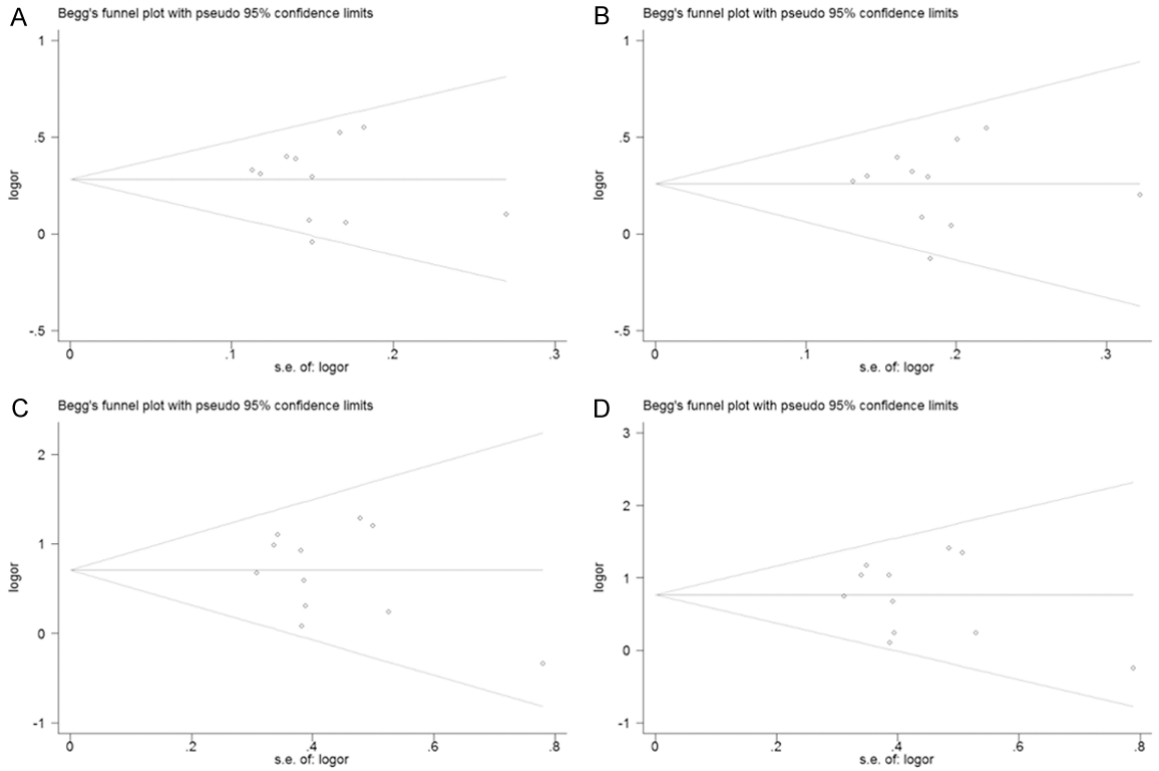

Figure 4. Publication bias for meta-analysis of rs712 polymorphism and Cancer risk in Chinese population. A. Allelic model (T vs G). B. Dominant genetic model (TT + GT vs GG). C. Recessive genetic model (TT vs GT + GG). D. Addictive genetic model (TT vs GG).

Table 4. Publication bias analysis of the meta-analysis

	Test	T	95% CI	*P* value
T vs G	Begg's Test			1.00
	Egger's test	-0.46	-5.18-3.42	0.66
TT + GT vs GG	Begg's Test			1.00
	Egger's test	-0.10	-3.79-3.48	0.92
TT vs GT + GG	Begg's Test			0.44
	Egger's test	-0.89	-4.72-2.05	0.40
TT vs GG	Begg's Test			0.53
	Egger's test	-0.76	-4.91-2.43	0.46

as a prognostic factorin various carcinomas [38, 39]. *KRAS* gene contains several let-7 binding sites, and polymorphisms in the let-7 binding site of *KRAS* gene affects the binding efficiency of let-7, modifying host's susceptibility to cancer [10, 40]. Recently, some studies focused on KRAS rs712 which contains binding site for let-7. Yan L found that T allele was correlated with increased risk of glioma compared with the G allele [28]. Li ZH reported that the T allele of rs712 was associated with increased risk of gastric cancer [17]. Pan XM found that individuals carrying TT genotype and T allele of rs712 had an increased risk of colorectal cancer, and Jiang QH, Dai Q showed similar results [14, 16, 18]. Ni SS found an association between rs712 polymorphism and risk of cervical cancer [27]. On the other hand, Pan XM reported that rs712 polymorphism might not associate with nasopharyngeal carcinoma risk [22]. Peng XB showed that rs712 was not significantly associated with increased risk for non-small celllung cancer [29]. Huang X did not observe significant association between rs712 polymorphism and breast cancer risk [19]. Therefore, we performed a comprehensive meta-analysis to clarify this association. Because only one eligible study concerning rs712 and risk of cancer in Caucasian population, and the majority was Chinese population, We only include articles investigating Chinese population in the present meta-analysis.

Our meta-analysis found significant association of rs712 with the overall cancer risk in the allel-

ic, dominant, recessive, and additive genetic models in Chinese population. The sensitivity analysis showed that the association between rs712 and the overall cancer susceptibility was robust in all four genetic models. Furthermore, no publication bias exited in any genetic model. These results suggest that our findings were robust and stable.

Several limitations were present in our meta-analysis. First, only Chinese population was included due to the few number concerning Caucasian population. Second, although 2906 cases and 3544 controls were selected in the meta-analysis, the sample size in each study or each type of cancer was very small. Third, we analyzed the overall cancer risk, but did not perform stratified analysis based on different cancer type. These limitations may lead to bias in our findings.

In summary, our meta-analysis suggested that rs712 was significantly associated with cancer risk in Chinese population. However, further studies with larger sample sizes, concerning gene-gene and gene-environment interactions, along with functional analysis in different ethnic populations are warranted to provide a more reliable estimation of the association between rs712 and cancer susceptibility.

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Disclosure of conflict of interest

None.

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