JBUON 2016; 21(4): 1016-1023
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Association of the HOTAIR rs4759314 polymorphism with cancer risk: a meta-analysis

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Summary

Purpose: *To explore the association between HOTAIR rs4759314 and cancer risk.*

Methods: *A comprehensive online search was conducted using PubMed, EMBASE, and CNKI databases to identify relevant studies. The case-control studies related to HOTAIR rs4759314 polymorphism and cancer risk were selected according to the inclusion and exclusion criteria. The retrieval time was until November 2015. After extracting the basic data information and performing an evaluation of the quality of the literature, the meta-analysis was performed using STATA 12.0 software, by calculating the odds ratio (OD) and 95% confidence interval (95% CI), and further subgroup analysis, literature publication bias testing, and sensitivity analysis.*

Results*: The studies included a total of 5025 patients with cancer and 5657 controls. The results found no significant association between the HOTAIR rs4759314 polymorphism and cancer risk in a Chinese population (G vs A, OR=1.06, 95% CI :0.87-1.30 ; GG/GA vs AA, OR=1.07, 95% CI: 0.87-1.32; GG vs GA/AA, OR=0.75, 95% CI:0.39-1.43; GA vs AA, OR=1.08, 95% CI: 0.88-1.33; GG vs AA, OR=0.76, 95% CI:0.39-1.45) (all p<0.05). However, A allelic gene was associated with lower risk of gastric cancer, while G allelic gene may act as a genetic susceptibility factor for gastric cancer in Chinese population.*

Conclusion: *No significant association was noted between the HOTAIR rs4759314 polymorphism and cancer risk in a Chinese population.*

Key words*: cancer susceptibility, HOTAIR rs4759314, meta-analysis, polymorphism*

Introduction

According to the most recent data [1], there were an estimated 14.1 million new cancer cases and 8.2 million deaths from cancer worldwide in 2012. Malignancies are a tremendous burden on the society both in developed and less developed countries. The details of the precise mechanism of tumorigenesis remain unknown. However, there are several known risk factors that are correlated with cancer mortality, including tobacco use, physical inactivity, and infection [2-4]. A growing number of studies demonstrated that genetic factors also play an important role in tumorigenesis [5-7] and evidence indicates that single nucleotide polymorphisms (SNPs), the most common genetic susceptibility factors, are associated with most cancer types [8-11].

Hox transcript antisense intergenic RNA, also called HOTAIR, is a well-studied, long non-coding RNA (lncRNA) [12,13]. A number of studies have shown that HOTAIR is correlated with the development and progression of a variety of malignancies [14-16]. The level of HOTAIR's expression in carcinomatous tissues is significantly higher than its level in adjacent tissues and normal tissue [17,18]. It is regarded as a novel biomarker of lymph node metastasis and

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Received: 009/12/2015; Accepted: 12/04/2016

poor prognosis in human cancers [19,20]. Many studies have explored the association between the rs4759314 polymorphism and cancer risk. However, the results are contradictory. Therefore, we performed this meta-analysis based on case-control studies to obtain more reliable conclusions and clarify the relationship of this polymorphism with cancer risk.

Methods

Search strategy

A comprehensive online search was conducted in PubMed, EMBASE, and China National

Knowledge Infrastructure (CNKI) databases to identify eligible studies. There was no language limitation used in the search, and the retrieval time was up to November, 2015. The following terms were used for the literature collection: ('hox transcript antisense intergenic RNA' OR 'HOTAIR' OR 'rs4759314') AND ('cancer' OR 'carcinoma' OR 'tumor' OR 'neoplasm') AND ('polymorphism' OR 'SNPs'). In addition, we obtained additional relevant publications by checking the reference lists. The flow chart of the search strategies is illustrated in Figure 1.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) all of the case-control studies investigated the association between HOTAIR rs4759314 polymorphism and cancer risk; (2) cancer diagnosis was confirmed by pathology and the control subjects were healthy or cancer-free volunteers; and (3) the publications included the basic information with sufficient data recorded.

Exclusion criteria were as follows: (1) Non-case-control studies; (2) studies investigating the molecular mechanism, structure, or functions of HOTAIR; (3) reviews, letters, or expert opinions; and (4) studies without usable data.

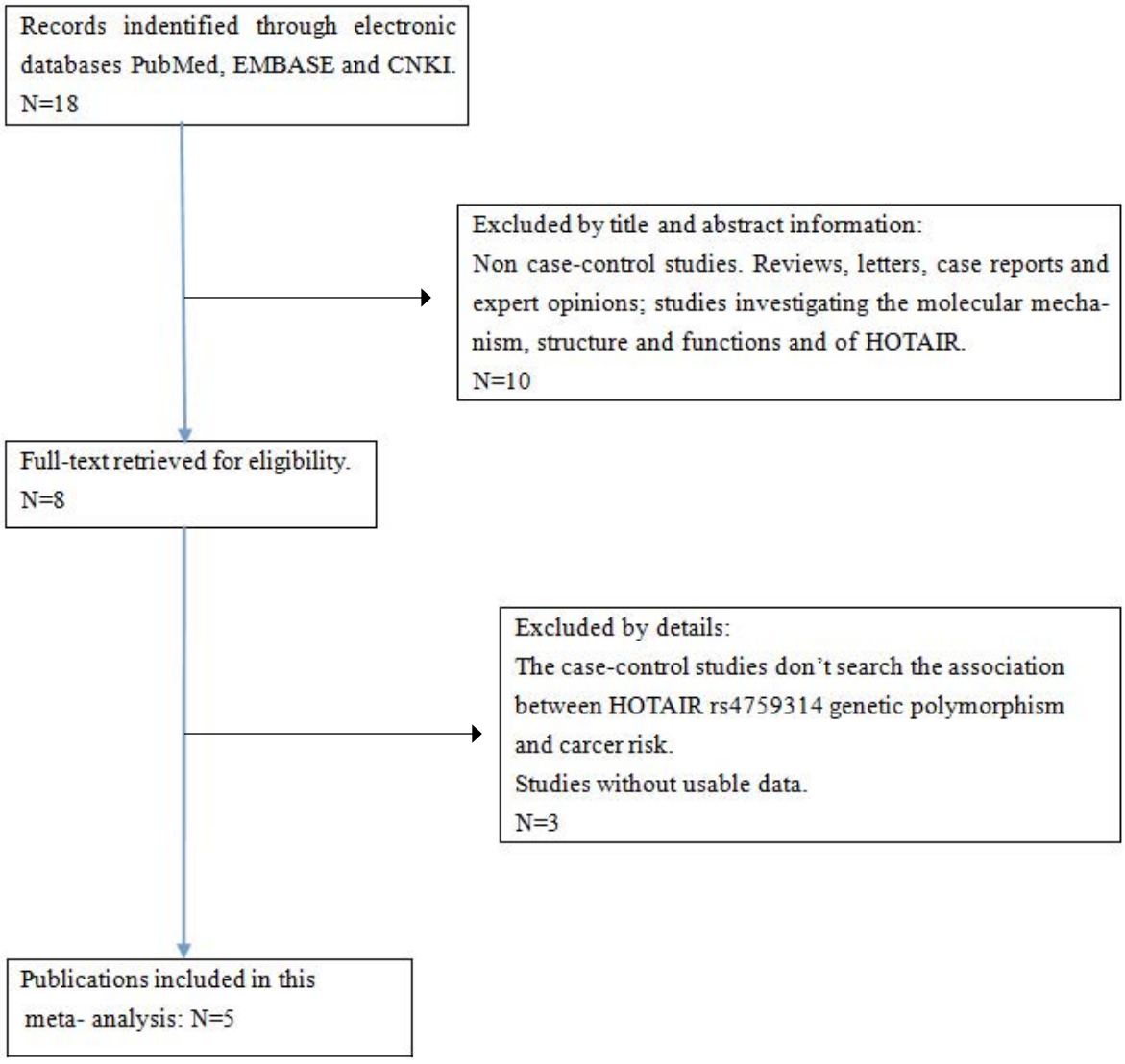

Figure 1. Flowchart presenting the steps of literature search and selection.

Data extraction

Two investigators (QC and XGF) extracted data from the eligible studies independently, according to the above inclusion and exclusion criteria. In case of disagreement, a decision was made by a third investigator (ZL). From each study, the following basic information and data were extracted: first author, year of publication, country, race, cancer type, study design, the number of cases and controls, genotype distribution, genotyping method, and P for Hardy–Weinberg equilibrium (HWE) in controls.

Assessment of study quality

The quality of the included studies was assessed by two reviewers (QC and XGF) according to a set of criteria described by Wang et al. [21]. A total of 5 aspects were included in the predetermined criteria as follows: the source of cases and controls, case-control matching, the source of obtained specimens used for the determination of genotypes, total sample size, and evidence of HWE. In case of disagreement, a decision was made by the third investigator (ZL). The quality of the studies was scored from 0 to 18, with higher scores indicating a better quality (high quality≥12, low quality <12).

Statistics

Statistical analyses were performed by using Stata 12.0. The heterogeneity between different studies was assessed using Q-statistic and the I^2 test [22]. If the heterogeneity was significant ($p \leq 0.1$, $I^2>50\%$), the random effects model was used [23], otherwise, the fixed effects model was used [24]. The pooled OR and 95% CI of all 5 genetic models were calculated individually.

Results

Characteristics of the studies

A total of 5 articles (including 7 case-control studies) were included in the meta-analysis [25-29]. The studies included a total of 5025 patients with cancer and 5657 control subjects. All studies were performed in China, and the participants were Chinese people. The genotype frequencies of the controls were all in accordance with HWE. The quality score of 7 case-control studies ranged from 12-15, classified as high quality (≥12). The main characteristics and quality scores of the 7 case-control studies are summarized in Table 1.

Meta-analysis results

There was no association between the HOTAIR rs4759314 genetic polymorphism and the susceptibility to cancer in Chinese populations (G vs A, OR=1.06, 95% CI:0.87-1.30; GG/GA vs AA, OR=1.07, 95% CI:0.87-1.32; GG vs GA/AA, OR=0.75, 95% CI: 0.39-1.43; GA vs AA, OR=1.08, 95% CI: 0.88-1.33; GG vs AA, OR=0.76, 95% CI:0.39-1.45) (Table 2 ; all p>0.05).

In the subgroup analysis, negative association was noted between HOTAIR rs4759314 genetic polymorphism and the risk of digestive tract tumor or breast cancer. In the subgroup of genotyping method no association was found between HOTAIR rs4759314 polymorphism and cancer risk in PCR-RFLP or TaqMan.

In the subgroup of cancer type, a significant association was shown in the allele model (G vs A), the dominant genetic model (GG/GA vs AA), and the co-dominant model (GA vs AA) (Table 2 and Figures 2-4) (all p<0.05). This indicated that in a Chinese population, the G allelic gene may act as a genetic susceptibility factor in gastric

Table 1. Main characteristics of the studies included in the meta-analysis

First author, year	*Country*	*Race*	*Cancer type*	*Source of controls*	*Genotyping method*	*Cases/ Controls*	*Case genotypes*			*Control genotypes*			P_{HWE}	*Score*
							AA	AG	GG	AA	AG	GG		
Zhang,2014	China	Asian	ESCC	HB	PCR-RFLP	1000/1000	917	81	2	910	89	1	0.436	15
Du,2015	China	Asian	GC	HB	TaqMan	753/1057	624	126	3	915	136	6	0.699	15
Du,2015	China	Asian	GC	HB	TaqMan	522/587	459	60	3	549	36	2	0.098	15
Guo,2015	China	Asian	GC	HB	PCR-RFLP	515/654	461	53	1	589	64	1	0.587	15
Yan,2015	China	Asian	BC	HB	PCR-RFLP	502/504	451	50	1	448	54	2	0.785	15
Xue,2015	China	Asian	CRC	HB	TaqMan	1147/1203	1011	135	1	1037	157	9	0.259	12
Xue,2015	China	Asian	CRC	HB	TaqMan	586/652	517	65	4	571	79	2	0.673	12

HB: hospital-based HWE: Hardy-Weinberg equilibrium,
ESCC: esophageal squamous cell carcinoma, BC: breast cancer, GC: gastric cancer, CRC: colorectal cancer,
PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism

Table 2. Results of meta-analysis for the association between HOTAIR rs4759314 polymorphism and the susceptibility to cancer

Group (No. of studies)	*G vs A*		*GG/GA vs AA*		*GG vs GA/AA*		*GA vs AA*		*GG vs AA*	
	OR(95%CI)	I^2	*OR(95%CI²)*	I^2	*OR(95%CI²)*	I^2	*OR(95%CI²)*	I^2	*OR(95%CI²)*	I^2
Total (6)	1.06(0.87-1.30)	65.4	1.07(0.87-1.32)	64.5	0.75(0.39-1.43)	6.5	1.08(0.88-1.33)	62.5	0.76(0.39-1.45)	7.8
Type										
BC(1)	0.89(0.61-1.31)	-	0.90(0.61-1.35)	-	0.50(0.05-5.54)	-	0.92(0.61-1.38)	-	0.50(0.04-5.5)	-
Dtt(6)	1.09(0.87-1.37)	70.1	1.10(0.87-1.39)	69.3	0.77(0.39-1.52)	19.5	1.11(0.88-1.39)	67.7	0.78(0.40-1.54)	20.5
GC(3)	1.35(1.01-1.81)	57.4	1.39(1.02-1.89)	57.7	1.01(0.37-2.72)	0.0	1.40(1.02-1.19)	56.9	1.05(0.39-2.85)	0.0
Method										
PCR-RFLP(3)	0.96(0.78-1.17)	0.0	0.95(0.78-1.17)	0.0	1.06(0.27-4.26)	0.0	0.95(0.77-1.17)	0.0	1.06(0.26-4.24)	0.0
TaqMan(4)	1.15(0.82-1.61)	81.2	1.18(0.83-1.66)	80.2	0.68(0.32-1.42)	47.3	1.19(0.85-1.66)	78.5	0.69(0.33-1.45)	48.4

I^2 for heterogeneity test, OR : odds ratio, CI : confidence interval, Dtt: digestive tract tumor

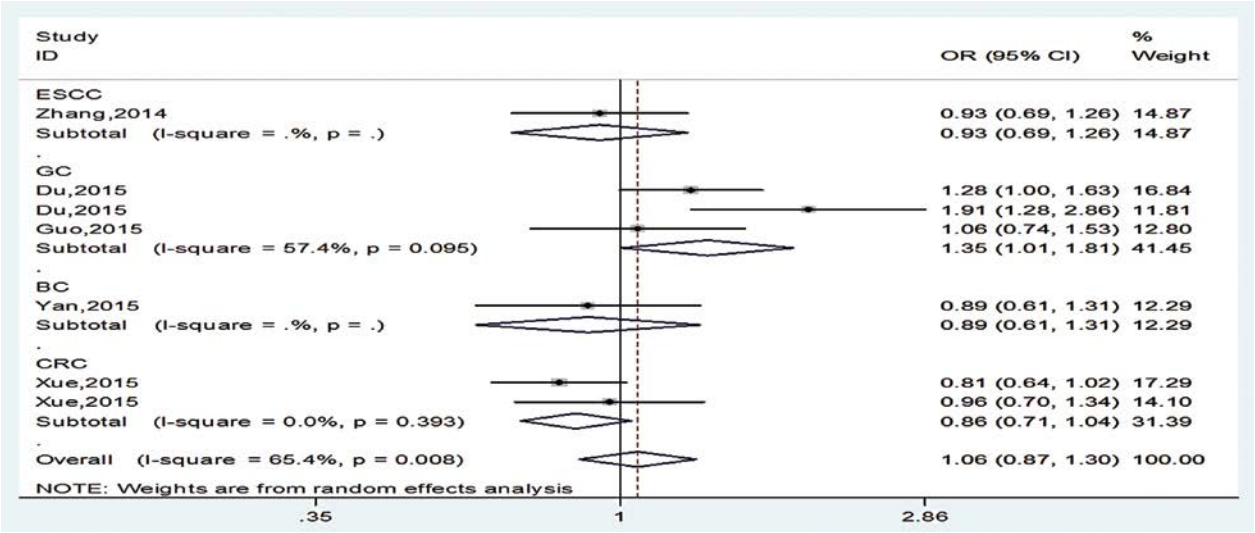

Figure 2. Forest plot of the association between the HOTAIR rs4759314 polymorphism and cancer risk under the allele model (G vs A).

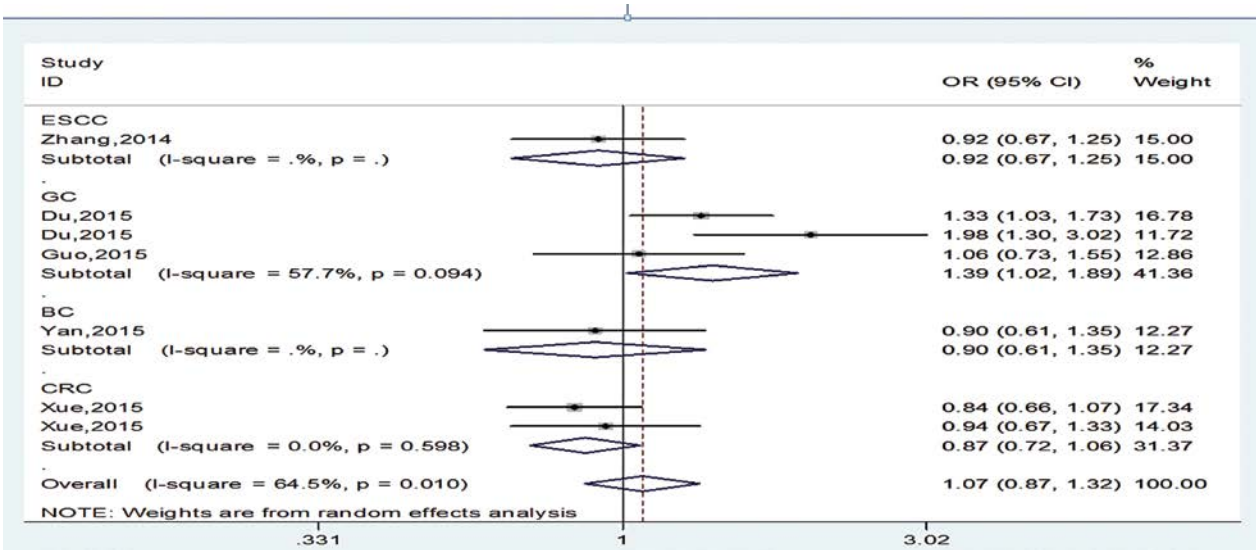

Figure 3. Forest plot of the association between the HOTAIR rs4759314 polymorphism and cancer risk under dominant genetic model (GG/GA vs AA).

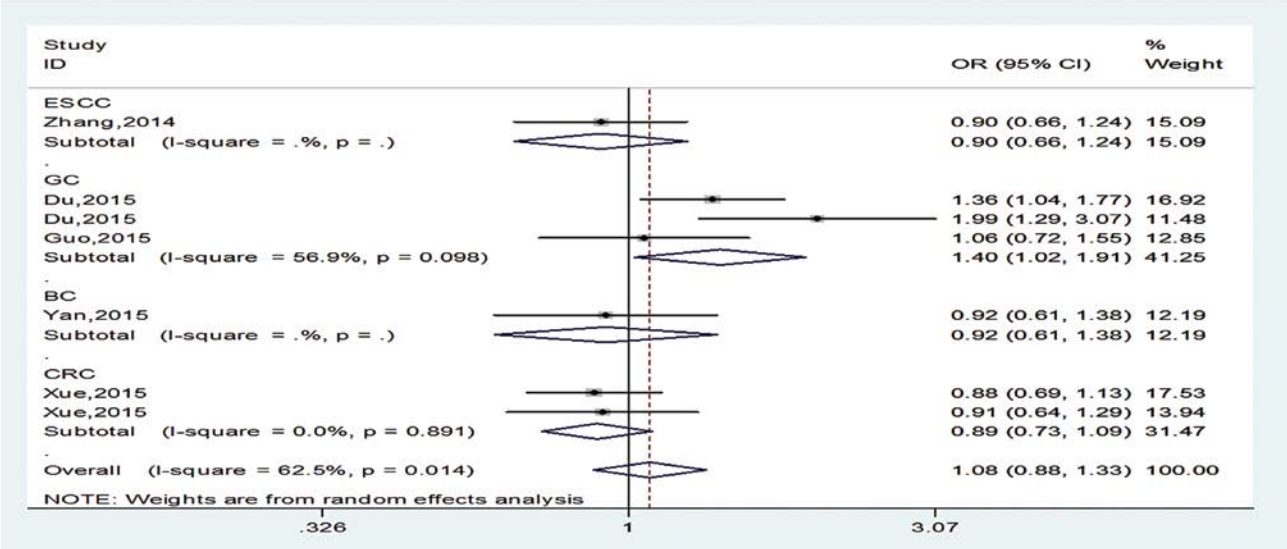

Figure 4. Forest plot of the association between the HOTAIR rs4759314 polymorphism and cancer risk under codominant model (GA vs AA).

cancer, while A allelic gene may reduce the risk of gastric cancer.

Sensitivity analysis

Sensitivity analysis was conducted by omitting each study in turn from the pooled analysis to examine the influence of the removed data set on the pooled OR. Exclusion of each study did not influence the result of specific genotype comparison for rs4759314, suggesting the robustness of the results (Figures 5-7).

Publication bias

Each genetic model was individually tested for bias by funnel plot (not shown), Egger's linear regression test and Begg's rank correlation method. The results revealed no publication bias for the included studies (Table 3).

Discussion

This study examined whether the rs4759314 polymorphism has an association with cancer risk. To the best of our knowledge, this is the first meta-analysis addressing the association between HOTAIR rs4759314 polymorphism and cancer susceptibility. Many studies reported that lncRNA, RNAs longer than 200 nucleotides in length [30,31], play important roles in a wide range of biological processes [32,33]. HOTAIR is one of the best known lncRNA, and has been shown to influence tumorigenesis. Aberrant overexpression of HOTAIR is positively correlated with proliferation and invasion in cancer cells as well as prognosis in patients with cancer [34-36].

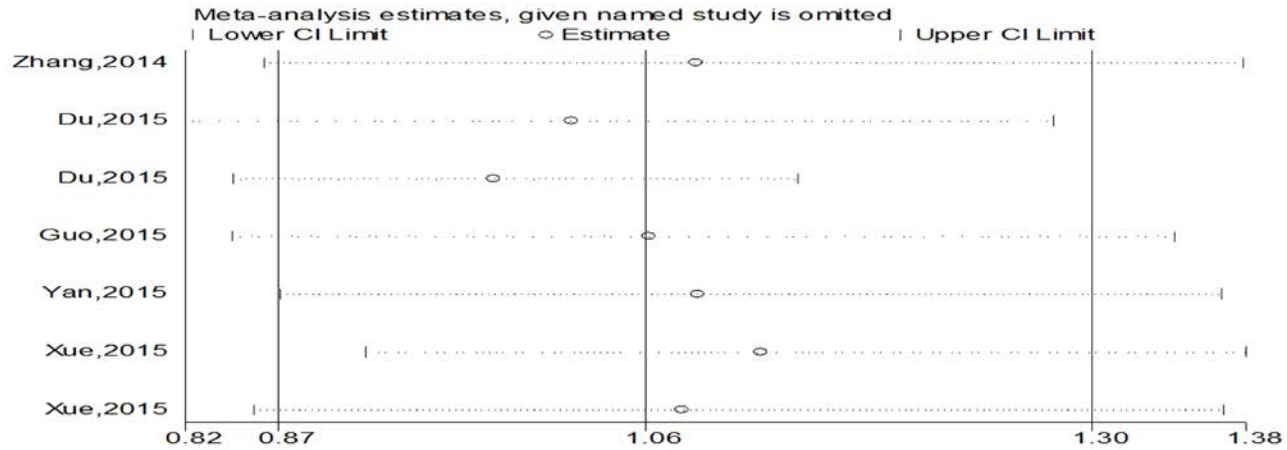

Figure 5. Sensitivity analysis under the allele model (G vs A) of HOTAIR rs4759314 polymorphism.

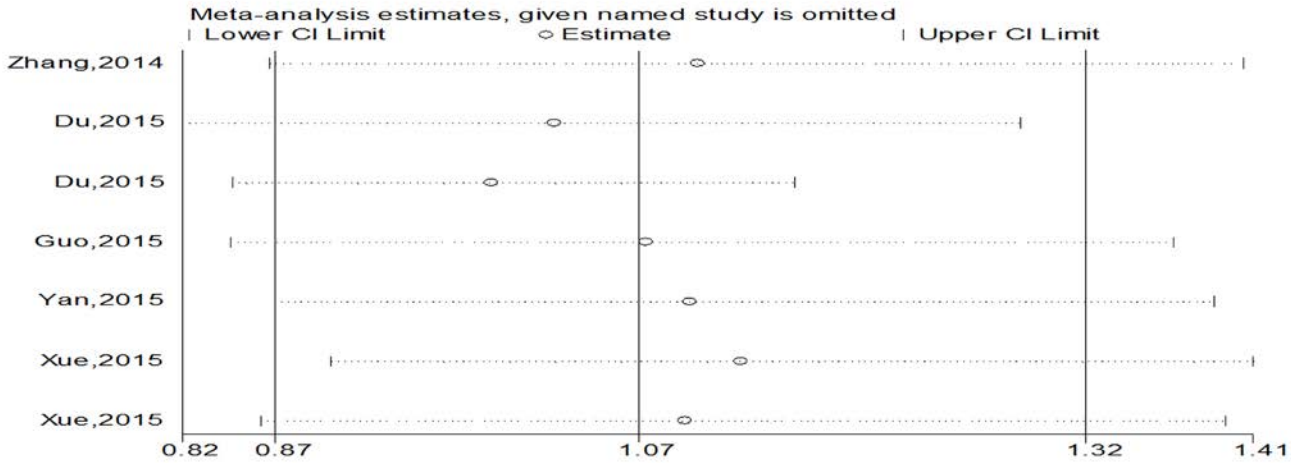

Figure 6. Sensitivity analysis under the dominant genetic model (GG/GA vs AA) of HOTAIR rs4759314 polymorphism.

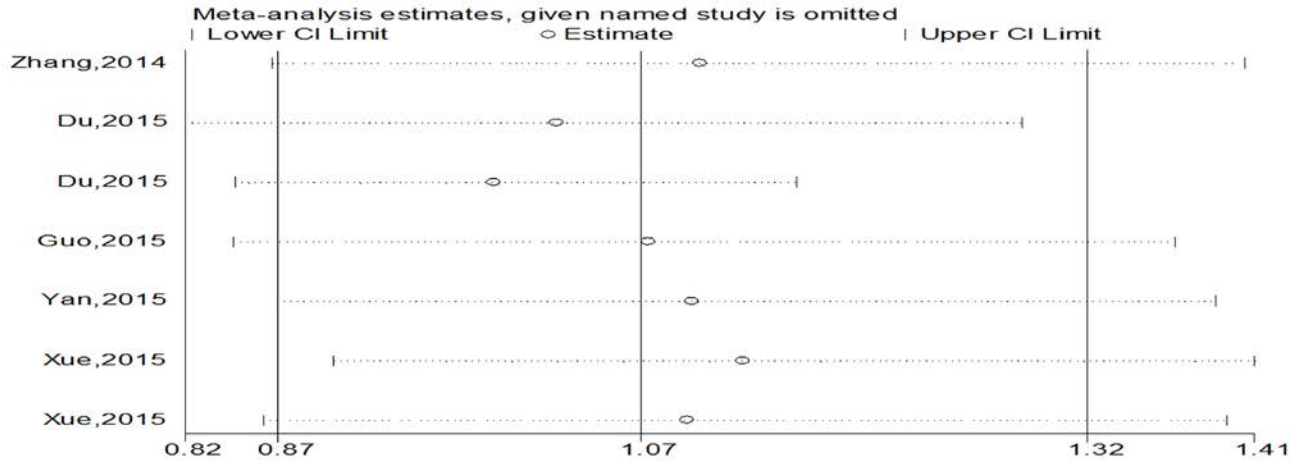

Figure 7. Sensitivity analysis under the codominant model(GA vs AA) of HOTAIR rs4759314 polymorphism.

Table 3. The results of Egger's test and Begg's test for publication bias

Models	*G vs A*	*GG/GA vs AA*	*GG vs GA/ AA*	*GG vs AA*	*GA vs AA*
Methods					
Egger's test (P/95%CI)	0.422(-5.445-11.054)	0.477(-5.919-10.961)	0.908(-5.089-4.632)	0.878(-5.197- 4.581)	0.554(-6.264- 10.360)
Begg's test (Z/P value)	1.05/0.293	1.35/0.176	-0.75/0.453	-0.75/0.453	1.65/0.099

Nevertheless, the exact mechanism that regulates HOTAIR expression is unclear, and the genetic impact of HOTAIR on cancer susceptibility and patient prognosis is still unknown.

This study revealed no significant association between the rs4759314 polymorphism and cancer risk in Chinese populations. We found negative association between HOTAIR rs4759314 genetic polymorphism and susceptibility to digestive tract tumor or breast cancer as well as in the subgroup. However, a significant association was found between the rs4759314 polymorphism and gastric cancer, suggesting that A allelic gene may decrease risk to GC in a Chinese population.

There are a few limitations of this meta-analysis. Firstly, all included studies were hospital-based and there may be inherent choice bias. Therefore, inclusion of population-based studies should be done to verify our results. Secondly, the total sample size of our analysis is rather limited, and consisted of only Chinese subjects. Prospective case–control studies with a more diverse population and larger sample

size are needed to ascertain the association between HOTAIR rs4759314 polymorphism and cancer risk. Thirdly, the association between rs4759314 polymorphism and different cancer types may differ and further research with a larger number of subjects should be carried out to assess the relationship of rs3783553 polymorphism with specific types of cancer, particularly GC.

In conclusion, the meta-analysis we performed revealed that HOTAIR rs4759314 genetic polymorphism was not related to cancer risk in Chinese populations. There may be a significant association between the rs4759314 polymorphism and GC. Certainly, a larger-size,multi-center and higher-quality studies are required to further test these findings in the future.

Conflict of interests

The authors declare no confict of interests.

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