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Original Article

Association between LncRNA HOTAIR rs4759314 A > G polymorphism and cancer risk: a meta-analysis based on 5525 cases and 6657 controls in Chinese populations

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Abstract: Emerging evidence shows that long non-coding RNA (LncRNA) function as tumor suppressors or oncogenes in human carcinogenesis. Single nucleotide polymorphism (SNP) causes the amino acid alteration of LncRNA HOTAIR and might have a physiologic effect on cancer development. However, previous studies showed conflicting results regarding the association of HOTAIR rs4759314 A > G polymorphism with cancer. A computerized search of PubMed, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) for publications on HOTAIR rs4759314 A > G polymorphism and cancer risk was performed and the genotype data were analyzed in a meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the association. There was no significant association between HOTAIR rs4759314 A > G polymorphism and overall cancer risk in the comparison models. Moreover, subgroup analysis revealed that the variant AG (OR=1.29, 95% CI=1.06-1.57) and AG/GG (OR=1.28, 95% CI: 1.06-1.55) genotypes were associated with an increased risk of gastric cancer (GC) compared with wild-type AA genotype. The results suggest that HOTAIR rs4759314 polymorphism may play a role in gastric cancer susceptibility in Chinese populations based on current studies. Further large-scale studies and functional studies between this polymorphism and cancer risk are warranted.

Keywords: LncRNA, HOTAIR, polymorphism, cancer, meta-analysis

Introduction

Over the last decades, researchers have been exploring novel, long noncoding RNAs (LncRNAs) to characterize their potential roles in cancer development and biological processes [1-3]. Noncoding RNAs (ncRNAs) are emerging as new regulators in the cancer paradigm. It has been demonstrated that potential roles in both oncogenic and tumor suppressive pathways [4, 5]. LncRNAs play a crucial role in various key biological processes that include alternative splicing, genomic imprinting, gene regulation, and chromatin organization. The dysregulation of LncRNAs can lead to poor patient outcome, prognosis and cancer metastasis [6].

Although LncRNAs appear to be critical for various biological processes, their mechanism of action and transcriptional regulation still remains elusive. LncRNAs are non-protein coding transcripts longer than 200 nucleotides and are implicated in some important events, such as transcriptional regulation, epigenetic regulation, and post-transcriptional regulation [7, 8]. LncRNA HOX transcript antisense RNA (HOTAIR) involved in development and progression of multiple cancers is expressed from the homebox C gene (HOXC) locus. It has been found that overexpression of HOTAIR is significantly associated with several human carcinomas such as pancreas [9], liver [10], gastric cancer [11, 12], esophageal cancers [13, 14], breast [15], colon [16], lung [17, 18], laryngeal [19], nasopharyngeal [20], and so on. Recently, several studies have evaluated the relationship between HOTAIR polymorphism and human cancer risk [21-28]. However, the results of these studies

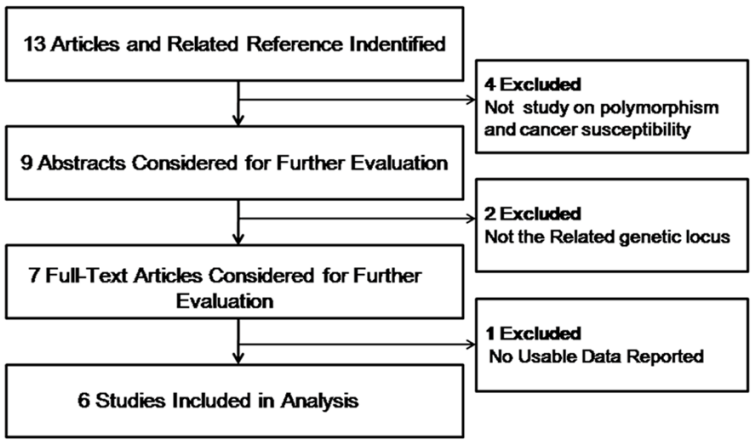


Figure 1. Studies identified with criteria of inclusion and exclusion.

are inconclusive. Here, we performed a meta-analysis to precisely characterize whether or not HOTAIR polymorphism is associated with human cancer risk.

Materials and methods

Publication search

We searched the PubMed, Web of Science, and Chinese National Knowledge Infrastructure databases (last updated on Dec 1th, 2015) for published studies on the relationship of HOTAIR polymorphism with cancer risk. The following keywords were used either separately or together: "HOTAIR", "polymorphism or mutation", and "cancer or tumor." The references of related studies were reviewed to search other potentially related articles manually. All of the selected studies in our meta-analysis should also match the following inclusion criteria: (1) human case-control study (2); evaluation of HOTAIR rs4759314 polymorphism and cancer risk; and (3) availability of genotype frequencies in the study. We also restricted our search to studies published in English and Chinese. The procedures of database search are shown in **Figure 1**.

Data extraction

Two investigators independently obtained the following information from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity; (5) cancer type; (6) total number of control subjects and cases; (7) genotype frequencies for cases and control subjects; and (8) Hardy-Weinberg equilibrium (HWE) of control subjects. Differences in the findings of the investigators were resolved by discussion.

Statistical analysis

HWE was calculated for the control subjects of each study by using a Chi-square goodness-of-fit test. Studies with inconsistent HWE ($P< 0.05$) were removed. The STATA software (version 12.0; Stat Corporation, College Station, Texas, USA) was used to conduct the statistical analysis; all of the tests were two-sided. The OR and 95% confidence interval (CI) were used to evaluate the strength of the association between the HOTAIR polymorphism and cancer risk. We determined the relationship between SNP and cancer susceptibility by using the following genetic models: homozygote model (GG/AA); heterozygote model (AG/AA); the dominant genetic model (AGGG/AA); and recessive genetic model (GG/AAAG). Subgroup analyses were also conducted according to cancer type. The Z test was used to determine the significance of the pooled OR, in which the results were considered statistically significant at $P<0.05$. The heterogeneity among studies was determined by using a Chi-square-based Q test. The fixed-effect model (Mantel-Haenszel model) was used when homogeneity was considered significant ($P > 0.05$); otherwise, the random-effect model (DerSimonian and Laird method) was used. In addition, publication bias was assessed using Begg's funnel plot and Egger's test ($P<0.05$ was considered a significant publication bias). These procedures were conducted twice in our meta-analysis.

Result

Characteristics of the studies

After an extensive search was conducted, a total of 6 studies (with 5525 cancer patients and 6657 control subjects) satisfied our criteria [21-25, 28]. The details of each study are shown in **Table 1**. Among these studies, three focused on gastric cancer (GC), and the other two focused on esophageal squamous cell carcinoma (EC) and colorectal cancer (CRC). The geno-

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

First autor	Years	Country	Ethnicity	Cancer	Cases	Controls	Case			Control			P_{WHE}
							AA	AG	GG	AA	AG	GG	
Zhang	2014	China	Asian	EC	1000	1000	917	81	2	910	89	1	0.44
Pan	2015	China	Asian	GC	500	1000	451	48	1	914	83	3	0.45
Wei	2015	China	Asian	GC	515	654	461	53	1	589	64	1	0.59
Du	2015	China	Asian	GC	1275	1644	1083	186	6	1464	172	8	0.23
Xue	2015	China	Asian	CRC	1733	1855	1528	200	5	1608	236	11	0.61
Yan	2015	China	Asian	BC	502	504	451	50	1	448	54	2	0.79

Abbreviations: HWE, Hard-Weinberg equilibrium; EC, Esophageal squamous cell carcinoma; GC, Gastric cancer; CRC, Colorectal cancer; BC, Breast cancer.

Table 2. Meta-analysis of LncRNA HOTAIR rs4759314 A > G polymorphism and cancer risk

Comparisons	Study	N[a]	Test of association			Test of heterogeneity			
			OR (95% CI)	Z	*P*-value	Model[b]	X^2	*P*[c]-value	I^2 (%)
GG/AA	Overall	6	0.75 (0.40-1.40)	0.91	0.36	F	1.90	0.86	0.0
	GC	3	0.97 (0.39-2.39)	0.07	0.94	F	0.14	0.93	0.0
AG/AA	Overall	6	1.06 (0.87-1.29)	0.57	0.57	R	12.64	0.03	60.4
	GC	3	1.29 (1.06-1.57)	2.51	0.01	F	2.47	0.29	19.1
AGGG/AA	Overall	6	1.05 (0.86-1.28)	0.48	0.63	R	12.98	0.02	61.5
	GC	3	1.28 (1.06-1.55)	2.56	0.01	F	2.35	0.31	15.0
GG/AAAG	Overall	6	0.74 (0.40-1.38)	0.95	0.34	F	1.77	0.88	0.0
	GC	3	0.93 (0.38-2.30)	0.15	0.88	F	0.14	0.93	0.0

[a]Number of comparisons; [b]Fix-effects model (F) was used when *P*-value for heterogeneity ≥0.05; otherwise, random-effects model (R) was used. [c]*P*-value of Q-test for heterogeneity test. Abbreviations: GC, Gastric cancer.

typic distributions in the control populations were consistent with HWE in the selected studies.

Quantitative synthesis and heterogeneity analysis

As shown in **Table 2**, for the HOTAIR rs4759314 polymorphism, all studies combined (5525 cases and 6657 controls) were pooled into the meta-analysis. Overall, no significant association between the HOTAIR rs4759314 polymorphism and cancer risk was observed in any genetic model (homozygote model: OR=0.75, 95% CI=0.40-1.40; heterozygote model: OR= 1.06, 95% CI=0.87-1.29; dominant genetic model: OR=1.05, 95% CI=0.86-1.28; and recessive genetic model: OR=0.74, 95% CI= 0.40-1.38). Intriguingly, the HOTAIR rs4759314 polymorphism showed evidence of an association with an increased risk for gastric cancer (heterozygote model: OR=1.29, 95% CI=1.06-1.57; dominant genetic model: OR = 1.28, 95% CI=1.06-1.55) (**Figure 2**).

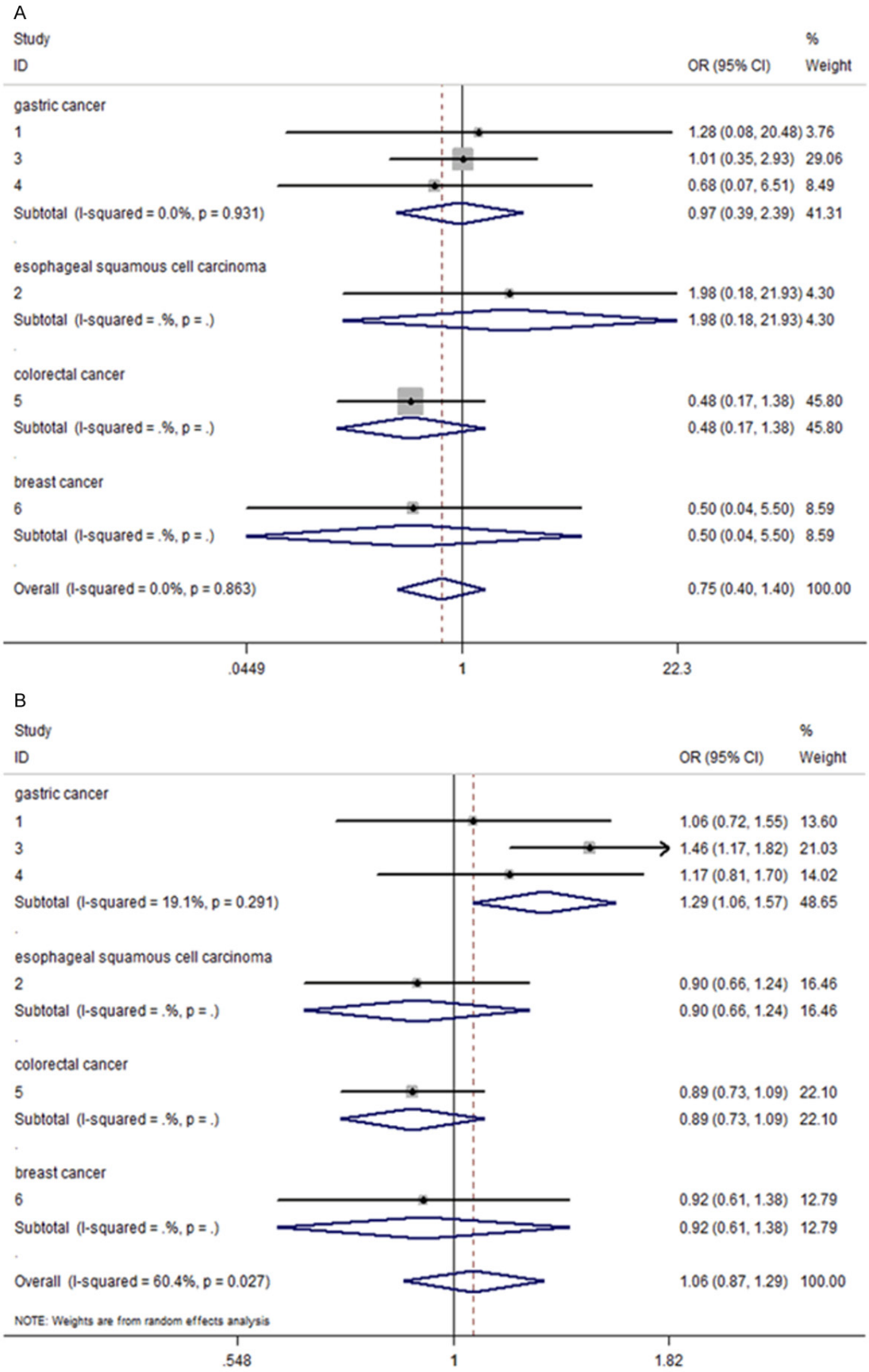
There was significant heterogeneity in the heterozygote model (AG versus AA: I^2=60.4%), and dominant model (AG/GG versus AA: I^2=61.5%). However, heterogeneity was not found in the homozygote and recessive model (GG versus AA: I^2=0.0%; GG versus AA/AG: I^2=0.0%). Next, the analysis stratified by tumor type was performed. Base on the lower I^2 values in subgroup (AG versus AA: I^2=19.1%; AG/GG versus AA: I^2=15.0%), we thought that tumor type was the main origin of heterogeneity.

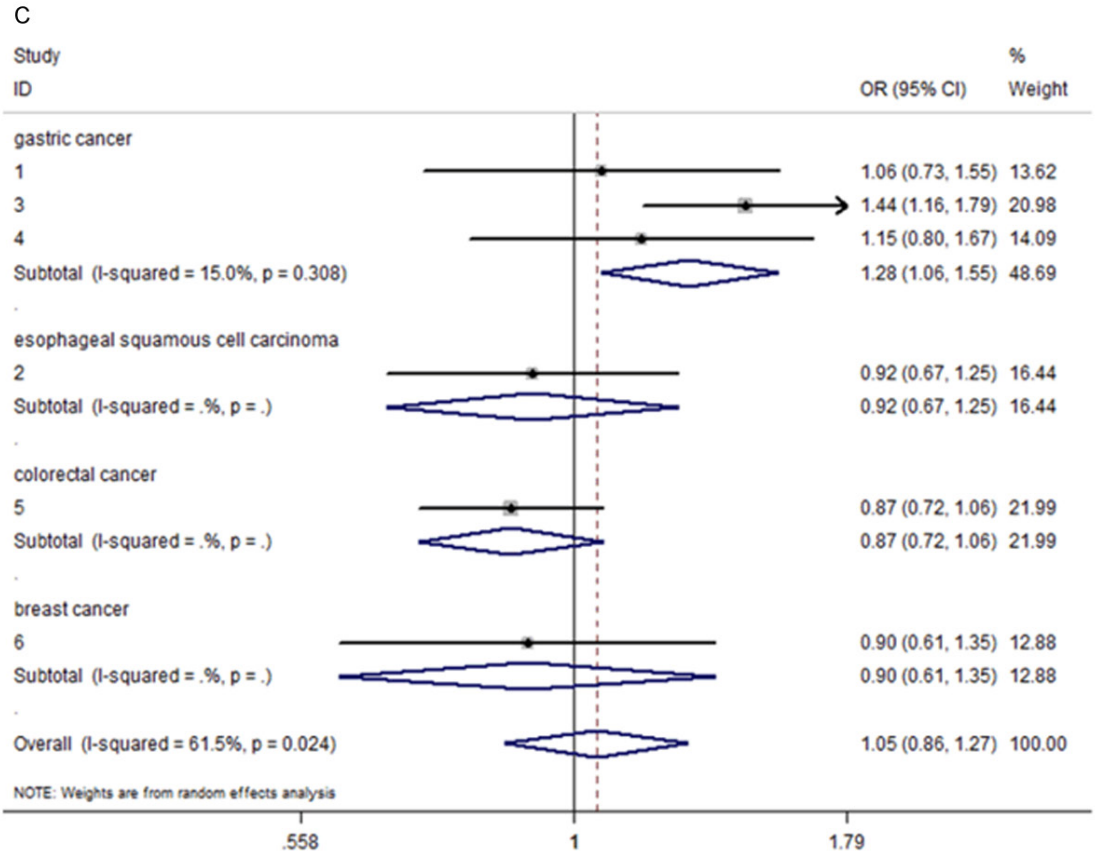
Publication bias

Publication bias was assessed by Begg's funnel plot and Egger's test (**Figure 3**). We found that the graphical funnel plots were symmetrical for the comparison of the genetic models. Egger's test results did not indicate any evidence of publication bias in our meta-analysis (P > 0.05).

Sensitivity analysis

Sensitivity analyses were performed after sequential removal of each eligible study. No single study changed the pooled overall ORs qualitatively, suggesting that the results were


A
Study
ID
OR (95% CI)
%
Weight
gastric cancer
1
1.28 (0.08, 20.48) 3.76
3
1.01 (0.35, 2.93) 29.06
4
0.68 (0.07, 6.51) 8.49
Subtotal (I-squared = 0.0%, p = 0.931)
0.97 (0.39, 2.39) 41.31
esophageal squamous cell carcinoma
2
1.98 (0.18, 21.93) 4.30
Subtotal (I-squared = .%, p = .)
1.98 (0.18, 21.93) 4.30
colorectal cancer
5
0.48 (0.17, 1.38) 45.80
Subtotal (I-squared = .%, p = .)
0.48 (0.17, 1.38) 45.80
breast cancer
6
0.50 (0.04, 5.50) 8.59
Subtotal (I-squared = .%, p = .)
0.50 (0.04, 5.50) 8.59
Overall (I-squared = 0.0%, p = 0.863)
0.75 (0.40, 1.40) 100.00
.0449
1
22.3
B
Study
ID
OR (95% CI)
%
Weight
gastric cancer
1
1.06 (0.72, 1.55) 13.60
3
1.46 (1.17, 1.82) 21.03
4
1.17 (0.81, 1.70) 14.02
Subtotal (I-squared = 19.1%, p = 0.291)
1.29 (1.06, 1.57) 48.65
esophageal squamous cell carcinoma
2
0.90 (0.66, 1.24) 16.46
Subtotal (I-squared = .%, p = .)
0.90 (0.66, 1.24) 16.46
colorectal cancer
5
0.89 (0.73, 1.09) 22.10
Subtotal (I-squared = .%, p = .)
0.89 (0.73, 1.09) 22.10
breast cancer
6
0.92 (0.61, 1.38) 12.79
Subtotal (I-squared = .%, p = .)
0.92 (0.61, 1.38) 12.79
Overall (I-squared = 60.4%, p = 0.027)
1.06 (0.87, 1.29) 100.00
NOTE: Weights are from random effects analysis
.548
1
1.82


C
Study
ID
OR (95% CI)
%
Weight
gastric cancer
1
1.06 (0.73, 1.55) 13.62
3
1.44 (1.16, 1.79) 20.98
4
1.15 (0.80, 1.67) 14.09
Subtotal (I-squared = 15.0%, p = 0.308)
1.28 (1.06, 1.55) 48.69
esophageal squamous cell carcinoma
2
0.92 (0.67, 1.25) 16.44
Subtotal (I-squared = .%, p = .)
0.92 (0.67, 1.25) 16.44
colorectal cancer
5
0.87 (0.72, 1.06) 21.99
Subtotal (I-squared = .%, p = .)
0.87 (0.72, 1.06) 21.99
breast cancer
6
0.90 (0.61, 1.35) 12.88
Subtotal (I-squared = .%, p = .)
0.90 (0.61, 1.35) 12.88
Overall (I-squared = 61.5%, p = 0.024)
1.05 (0.86, 1.27) 100.00
NOTE: Weights are from random effects analysis
.558
1
1.79

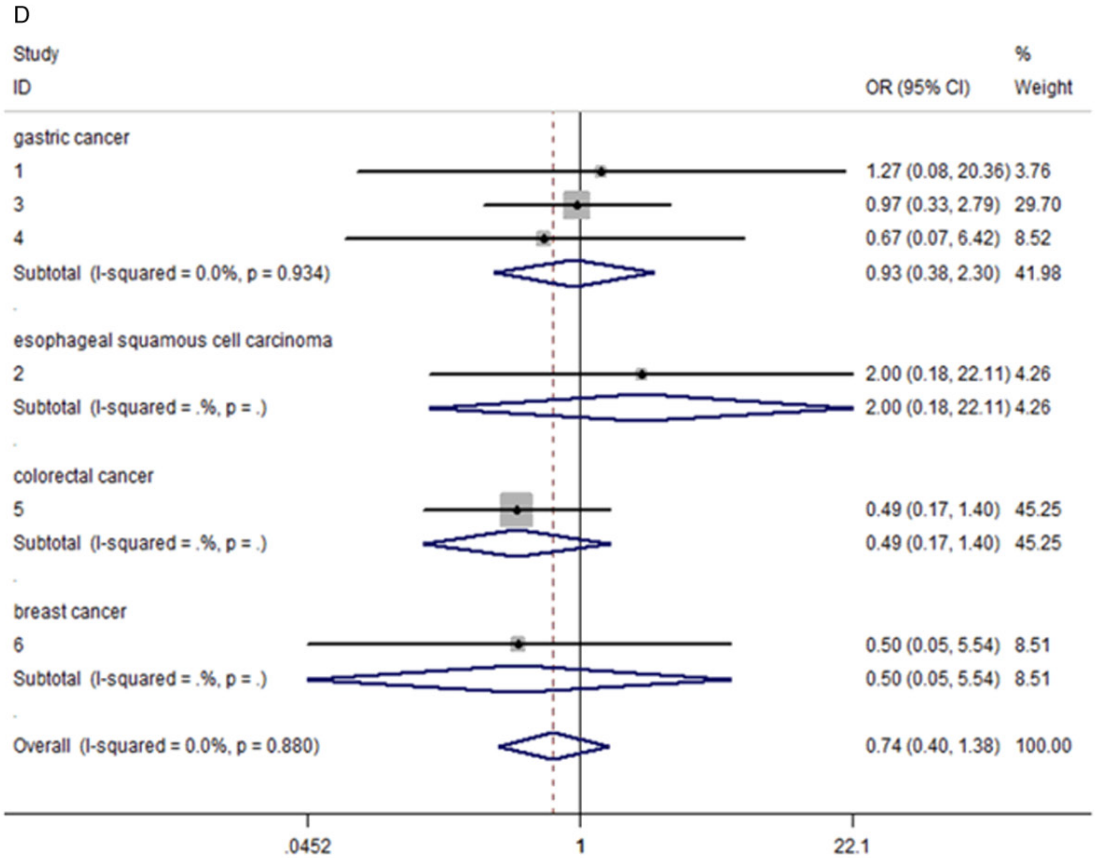

D
Study
ID
OR (95% CI)
%
Weight
gastric cancer
1
1.27 (0.08, 20.36) 3.76
3
0.97 (0.33, 2.79) 29.70
4
0.67 (0.07, 6.42) 8.52
Subtotal (I-squared = 0.0%, p = 0.934)
0.93 (0.38, 2.30) 41.98
esophageal squamous cell carcinoma
2
2.00 (0.18, 22.11) 4.26
Subtotal (I-squared = .%, p = .)
2.00 (0.18, 22.11) 4.26
colorectal cancer
5
0.49 (0.17, 1.40) 45.25
Subtotal (I-squared = .%, p = .)
0.49 (0.17, 1.40) 45.25
breast cancer
6
0.50 (0.05, 5.54) 8.51
Subtotal (I-squared = .%, p = .)
0.50 (0.05, 5.54) 8.51
Overall (I-squared = 0.0%, p = 0.880)
0.74 (0.40, 1.38) 100.00
.0452
1
22.1

Figure 2. Forest plot showing the stratified analysis performed according to cancer type. (A) GG/AA (B) AG/AA (C) AGGG/AA (D) GG/AAAG.

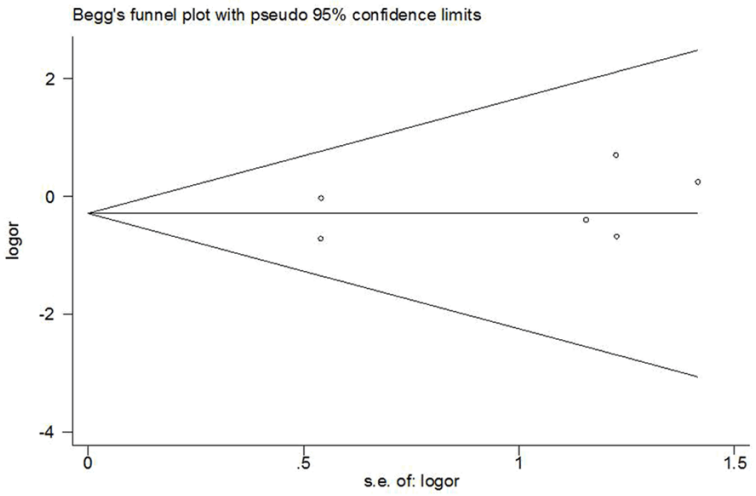


Figure 3. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log (OR): nature logarithm of OR. Horizontal line represents size of effect.

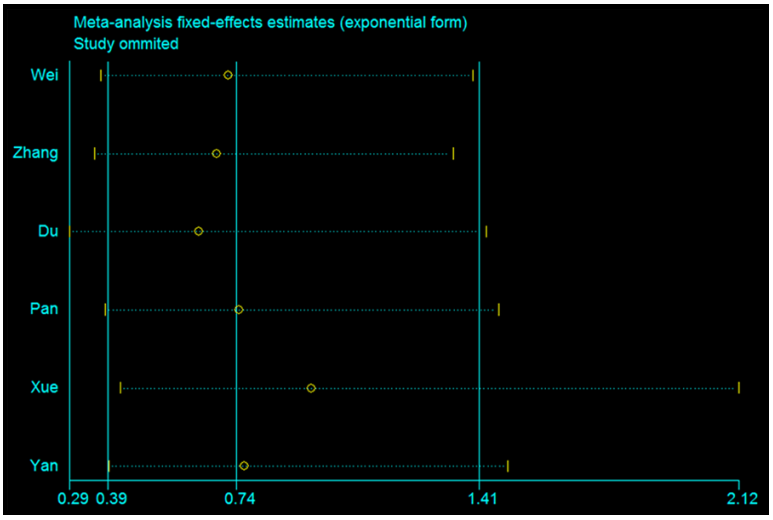


Figure 4. Sensitive analysis for the overall meta-analysis. This figure shows the influence of individual studies on the summary OR. The middle vertical axis indicates the overall OR and the two vertical axes indicate the 95% CI. Open circles indicate the pooled OR when the study indicated on the left is omitted from the meta-analysis. The lines indicate the 95% CI values when the study indicated is omitted from the meta-analysis.

stable (**Figure 4**). The significance of the ORs in the analysis stratified by tumor type was also not influenced by exclusion of any single study.

Discussion

It is well known that single nucleotide polymorphisms (SNPs) are the most common sources of human genetic variation, which may lead to an individual's susceptibility to cancer [29]. Some of these SNPs caused the amino acid alteration and might have a physiologic effect on cancer development which was involved in the non-synonymous variants. LncRNAs are emerging as a novel class of non-coding RNAs. Several lncRNAs have been identified as being linked to human disease and exerting specific functions [30]. Recent years, the number of studies investigating the relationship between LncRNA-HOTAIR polymorphism and the risk of human cancer has increased, while the interpretations of the phenotypic effects of this polymorphism are confusing and complicated. That means the results which have reported are confounding rather than conclusive.

It is feasible that the important difference in the findings of these studies may be owing to varieties of cancers, in consistencies in sample sizes, and dissimilarities of genotyping techniques as well as random errors. For instance, Wei Guo et al reported that only the T allele of rs12826786 of HOTAIR was found to increase the risk of developing GC and was associated with smoking habit and tumor-node metastasis (TNM) stage among three htSNPs of the HOTAIR gene (rs12826786 C > T, rs4759314 A > G, and rs10783618 C > T). Zhang and Pan et al also found that the HOTAIR rs4759314 A > G had no association with ESCC and GC risk in Chinese populations. However, Du et al identified that HOTAIR rs4759314 was significantly associated with the increased GC risk with an odds ratio (OR) of 1.39 (P=0.002). In our meta-analysis,

lack of association was found between the HOTAIR rs4759314 polymorphism and cancer susceptibility based on five case-control studies including 5,525 cancer patients and 6,657 control subjects. Subgroup analysis revealed that the variant AG and AG/GG genotypes were associated with an increased risk of GC compared with wild-type AA genotype.

Several possible limitations of the present meta-analysis should be acknowledged and taken into consideration. First, although the funnel plot and Egger's test showed no publication bias and although a exhaustive literature search was done, the numbers of published studies were not sufficiently enough for a comprehensive analysis on different types of cancer. Meanwhile, some publications and unpublished data were overlooked. Selection bias for the meta-analysis might have occurred. Secondly, detailed information was not available in all of the selected studies. A more precise analysis would be achieved if more detailed individual data were available, such as sex, mean age, control populations and exposure. Thirdly, in the subgroup analysis by cancer type, the number of studies and subjects analyzed for rs4759314 was small, and the statistical power was so weak that caution should be taken to interpret these results. A further investigation with much larger sample sizes is needed. In spite of these potential limitations, our meta-analysis also has some advantages. Firstly, The well-designed search and selection method significantly increased the statistical power of this meta-analysis. Secondly, studies included in our meta-analysis contained the distribution of the genotypes and available genotype frequency in the control population of all the studies were consistent with Hardy-Weinberg equilibrium. Thirdly, the stratified analysis reduced the heterogeneity found and the main origin of heterogeneity. Fourthly, no publication bias was detected among the pooled results. All in all, this mata-analysis indicated that the HOTAIR rs4759314 A > G variant was associated with an increased risk of GC. To confirm our results, we recommend that future well-designed studies and large sample size should consider diverse ethnic populations and cancer types.

Acknowledgements

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Disclosure of conflict of interest

None.

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