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Original Article

Quantitative assessment of the association between functional long non-coding RNA HOTAIR genetic variants and cancer susceptibility

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Abstract: Background: Epidemiological studies have indicated a significant association between lncRNA HOTAIR variants and cancer risk. But the conclusions were inconsistent. We therefore conducted a meta-analysis to explore the precise relationship between lncRNA HOTAIR polymorphisms and cancer risk. Methods: There online databases (PubMed, Embase, SCI) were searched. Odds ratios (ORs) and 95% confidence interval (CIs) were calculated to assess the associations between HOTAIR rs920778 C>T, rs4759314 A>G, rs1899663 G>T polymorphisms and cancer risk. Heterogeneity, publication bias and sensitivity analysis were performed to test the statistical power. Results: Overall, 6 related publications involving 11,961 subjects were included in our research. Significantly cancer risk between rs920778 C>T polymorphism were observed in general population (T vs. C: OR=1.33, 95% CI=1.13-1.56, P<0.01, I^2=75.0%; CT vs. CC: OR=1.24, 95% CI=1.03-1.49, P=0.02, I^2=63.5%; TT vs. CC: OR=2.03, 95% CI=1.25-3.30, P<0.01, I^2=80.5%; CT+TT vs. CC: OR=1.33, 95% CI=1.10-1.62, P<0.01, I^2=74.1%; TT vs. CC+CT: OR=1.97, 95% CI=1.34-2.90, P=0.01, I^2=46.3%). Subgroup analysis showed a significant increased risk in Asian population, but not in Caucasian population. For rs4759314 A>G and rs1899663 G>T polymorphisms, no significant association was detected with cancer risk. Conclusions: This meta-analysis demonstrates that lncRNA HOTAIR rs920778 C>T variant is an important risk factor for cancer development according to ethnicity diversity.

Keywords: Long non-coding RNA, Hox transcript antisense intergenic RNA, polymorphism, cancer

Introduction

Cancer is the leading cause of death in most countries, manifesting itself as a heavy physical, financial, and psychological burden on individuals as well as the society [1, 2]. In 2012, there were 14.1 million new cancer cases and 8.2 million deaths estimated worldwide [3]. Cancer development and treatment often accompanied with severe bodily dysfunctions, which related to low quality of living standards and poor five-year survival. Clinical researchers have established that lifestyle factors such as smoking, drinking, diet, physical inactivity, chronic inflammation, and viral infections are associated with cancer development [4, 5]. However, the underlying mechanisms contributing to cancer susceptibility is still unclear.

With the development of genomic technologies, studies on genetic factors have been gaining momentum, beginning from the late 20th century. Laboratory research has shown that genetic abnormalities influence the process of tumorigenesis by altering DNA transcription, translation, and eventually, protein expression [6]. Long non-coding RNAs (lncRNAs) are defined as long, single-stranded, non-coding RNAs with more than 200 nucleotides, lacking open reading frames (ORF) [7]. Studies have found that lncRNAs are involved in various essential life processes such as cell prolifera-

tion, differentiation, and apoptosis through transcriptional, post-transcriptional, and epigenetic regulation [8].

To date, thousands of lncRNA molecules have been identified in the human genome [9]. In particular, hox transcript antisense intergenic RNA (HOTAIR) is one of the most commonly studied lncRNA. It is located in the Homeobox C (HOXC) gene cluster on chromosome 12q13.13, with 2158 nucleotides [10]. Emerging evidence reveals that aberrant expression of lncRNA HOTAIR might influence normal cell cycle progression and promote cancer transformation [11, 12].

Genetic mutations, especially single nucleotide polymorphisms (SNPs) are considered the most important genetic variations, closely associated with tumorigenesis [13, 14]. Three common loci (rs920778 C>T, rs4759314 A>G, and rs1899663 G>T) have been reported in the lncRNA HOTAIR-encoding gene. These mutations play an important role in cancer development, treatment, and prognosis. This had been proved by several molecular epidemiological studies on cancers such as esophageal [15], gastric [16], colorectal [17], and breast cancers [18]. However, given the small sample sizes, the association between lncRNA HOTAIR polymorphisms and cancer risk is controversial. Bearing in mind the importance of lncRNA HOTAIR and cancer development, we conducted a meta-analysis to elucidate the association between the aforementioned lncRNA HOTAIR polymorphisms and cancer risks.

Materials and methods

This meta-analysis was designed and conducted according to the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA Compliant) statement [19].

Search strategy

Three online databases (PubMed, Embase, and SCI index) were searched to identify studies that focused on the association between lncRNA HOTAIR polymorphisms and cancer risk. The following search terms were used: “cancer”, “neoplasm”, “long non-coding RNA”, “Hox transcript antisense intergenic RNA”, “polymorphism”, and “variant”.

Eligible criteria

Studies that met the following criteria were included: 1) only case-control studies; 2) studies that revealed the relationship between lncRNA HOTAIR polymorphisms and cancer risk; 3) studies that provided sufficient information on genotype distribution to enable estimation of odds ratios (ORs) and 95% confidence intervals (CIs); 4) studies published in English alone; 5) only the study with the largest sample size or the most recent publication was included when overlapping data on similar patients emerged.

Exclusion criteria

We excluded these studies following: (1) the genotype distributions not reported and could not be ascertained or calculated; (2) the study subjects were not human; (3) animal models studies; and (4) review articles or case report.

Data extraction

Two independent investigators (Zhang and Shen) extracted the following information from the eligible studies: name of the first author, year of publication, country/region, ethnicity descent (Asian or Caucasian), controls design, sample size of cases and controls with different genotypes, genotyping method, Hardy-Weinberg equilibrium (HWE) for controls, and cancer type and quality score of the research.

Quality assessment

Two independent authors (Xu and Hu) assessed the quality of the included studies using a modified quality scoring criteria according to previous meta-analyses [20]. A 9-score system ranged from 0 points (worst) to 9 points (best) for genetic epidemiological studies based on traditional quality system was applied. Studies with 6 or higher score were considered as high quality, otherwise were considered as low quality.

Statistical analysis

All statistical analyses were performed using STATA version 11.0 (Stata Corporation, College Station, TX, USA). A P value less than 0.05 was considered statistically significant. Crude ORs with 95% CIs were calculated to estimate the

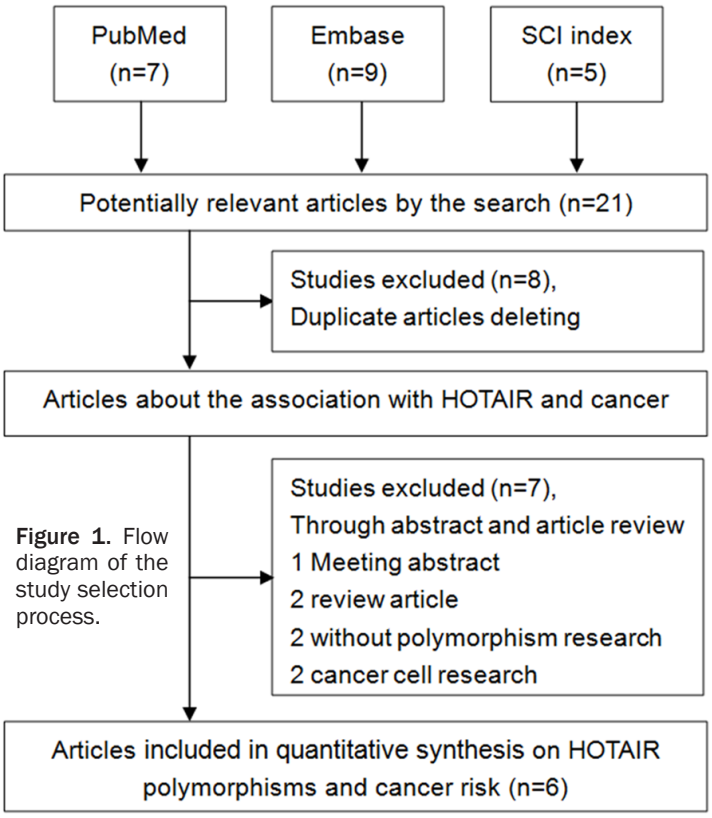

Figure 1. Flow diagram of the study selection process.

association between lncRNA HOTAIR polymorphisms (rs920778 C>T, rs4759314 A>G, rs1899663 G>T) and cancer risk. For example, pooled ORs were assessed for allele contrast (T vs. C) and codominant (CT vs. CC; TT vs. CC), dominant (CT+TT vs. CC), and recessive (TT vs. CC+CT) models in the rs920778 C>T polymorphism. Similar analyses for other genetic models (rs4759314 A>G andrs1899663 G>T) were also conducted. HWE in the controls was tested with chi-square test for goodness of fit, and P<0.05 was considered out of HWE. Subgroup analyses were conducted according to ethnicity, HWE status, study design, and genotyping method. Further, potential heterogeneity was examined with Chi-square-based Q-test and I-squared (I^2) statistics [21]. The random-effects model (DerSimonian and Laird method) was adopted when either the *P* value was less than 0.10 or I^2 was greater than 40% [22]. Otherwise, a fixed-effect model (the Mantel-Haenszel method) was used [23]. Cumulative meta- and sensitivity analyses were conducted to guarantee the stability of the results. Publication bias was analyzed by the Egger's linear regression and Begg's funnel plots [24, 25]. All *P*-values were two-sided with the P<0.05 considered statistically significant.

Results

Study characteristics

In total, 21 relevant articles were selected, following a systematic literature search. After gradual screening (**Figure 1**), six published articles involving 5,371 patients and 6,590 controls were included in the current meta-analysis (**Table 1**) [15-18, 26, 27]. Of these, four articles focused on Asian populations [15-17, 26], while two focused on Caucasians [18, 27]. Seven, five, and two case-control studies reported the association between cancer risk and rs920778 C>T [15, 18, 26, 27], rs4759314 A>G [15-17, 26], and rs1899663 G>T [15, 26] polymorphisms, respectively. With regard to the distribution of genotypes in the control groups, only one study deviated from HWE for thers920778 C>T polymorphism [26].

Quantitative analysis

Meta-Analysis Results for rs920778 C>T polymorphism: Seven case-control studies, involving 3,123 patients and 4,081 controls, explored the association between rs920778 C>T and cancer risk. The pool results indicated significantly increased risks for cancer development in all five genetic models (T vs. C: OR=1.33, 95% CI=1.13-1.56, P<0.01, I^2=75.0%; CT vs. CC: OR=1.24, 95% CI=1.03-1.49, P=0.02, I^2=63.5%; TT vs. CC: OR=2.03, 95% CI=1.25-3.30, P<0.01, I^2=80.5%; CT+TT vs. CC: OR=1.33, 95% CI=1.10-1.62, P<0.01, I^2=74.1%, **Figure 2**; TT vs. CC+CT: OR=1.97, 95% CI=1.34-2.90, P=0.01, I^2=46.3%) (**Table 2**). Subgroup analyses revealed similar results in Asian populations according to ethnicity (T vs. C: OR=1.47, 95% CI=1.35-1.59, P<0.01, I^2=27.1%; CT vs. CC: OR=1.33, 95% CI=1.19-1.47, P<0.01, I^2=2.1%; TT vs. CC: OR=2.89, 95% CI=2.30-3.64, P<0.01, I^2=0%; CT+TT vs. CC: OR=1.46, 95% CI=1.32-1.61, P<0.01, I^2=24.2%; TT vs. CC+CT: OR=2.58, 95% CI=2.06-3.32, P=0.01, I^2=0%) (**Table 2**). Furthermore, we also observed increased cancer risk in the hospital control group (**Table 2**).

Table 1. Characteristics of case-control studies on lncRNAHOTAIR polymorphisms and cancer risk included in the meta-analysis

First author	Year	Country/ Region	Racial	Source of controls	Case	Control	Genotype distribution						Genotyping methods	*P* for HWE[a]	MAF	Type	Quality score
							Case			Control							
							HOTAIR rs920778 C>T										
							CC	CT	TT	CC	CT	TT					
Zhang 1	2014	China	Asian	PB	1000	1000	528	389	83	601	358	41	PCR-RFLP	0.17	0.22	ESCC	7
Zhang 2	2014	China	Asian	PB	510	550	256	207	47	344	186	20	PCR-RFLP	0.40	0.21	ESCC	7
Zhang 3	2014	China	Asian	PB	588	600	307	230	51	378	205	17	PCR-RFLP	0.08	0.20	ESCC	7
Süleyman 1	2015	Turkish	Caucasian	HB	123	122	31	52	40	15	66	41	TaqMan	0.14	0.61	BC	8
Pan 1	2015	China	Asian	HB	500	1000	275	194	31	608	368	24	PCR-RFLP	<0.05	0.21	GC	8
Pan 2	2015	China	Asian	HB	300	600	145	127	28	372	207	21	PCR-RFLP	0.23	0.21	GC	9
Süleyman 2	2015	Turkish	Caucasian	HB	104	209	20	52	30	38	105	66	TaqMan	0.70	0.57	GC	8
							HOTAIR rs4759314 A>G										
							AA	AG	GG	AA	AG	GG					
Zhang 1	2014	China	Asian	PB	1000	1000	917	81	2	910	89	1	PCR-RFLP	0.44	0.05	ESCC	7
Guo	2015	China	Asian	HB	515	654	461	53	1	589	64	1	PCR-RFLP	0.59	0.05	GC	8
Pan 1	2015	China	Asian	HB	500	1000	451	48	1	914	83	3	PCR-RFLP	0.45	0.05	GC	9
Xue 1	2015	China	Asian	PB	1147	1203	1011	135	1	1037	157	9	Real-time PCR	0.26	0.07	CRC	8
Xue 2	2015	China	Asian	PB	586	652	517	65	4	571	79	2	Real-time PCR	0.67	0.06	CRC	8
							HOTAIRrs1899663 G>T										
							GG	GT	TT	GG	GT	TT					
Zhang 1	2014	China	Asian	PB	1000	1000	725	256	19	724	250	26	PCR-RFLP	0.43	0.15	ESCC	7
Pan 1	2015	China	Asian	HB	500	1000	376	118	6	732	255	13	PCR-RFLP	0.08	0.14	GC	9

[a]HWE in control; MAF: Minor allele frequency in control group. ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; BC: breast cancer; CRC: colorectal cancer; PB: Population-based; HB: Hospital-based.

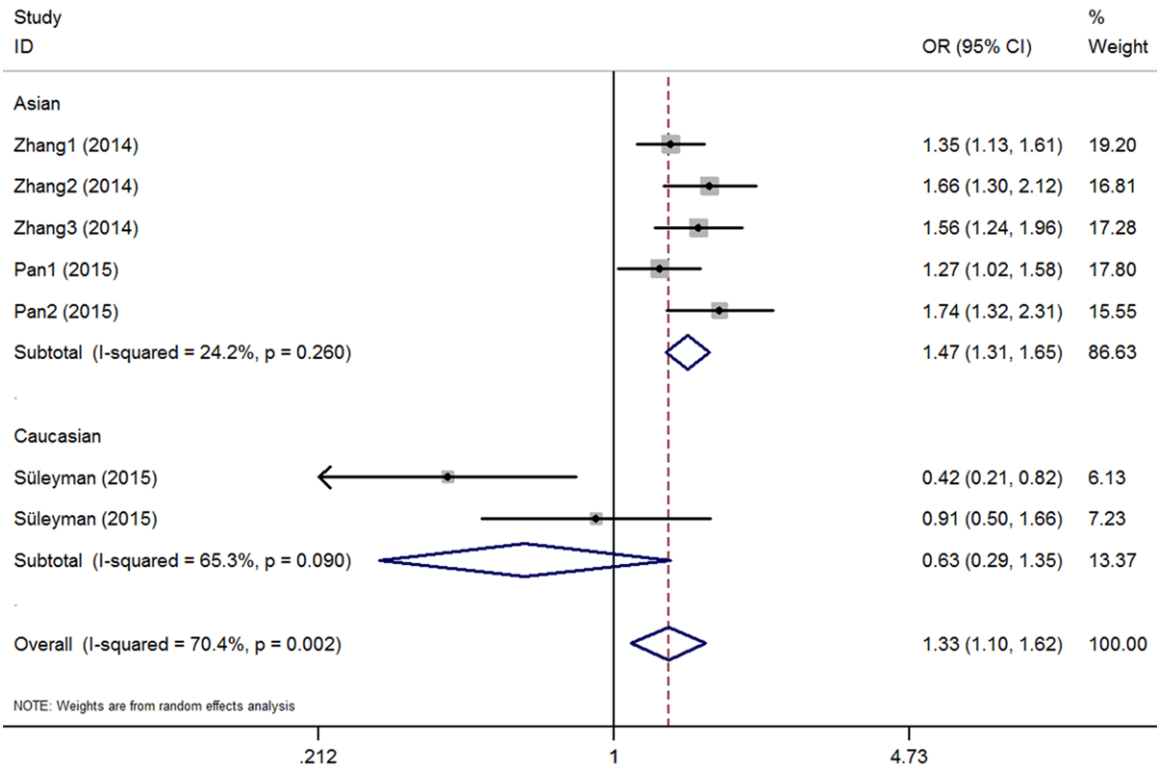

Figure 2. Calculated OR and 95% CIs for the associations between lncRNAHOTAIRrs920778 C>T polymorphism and cancer risk in the CT+TT vs. CC model.

Heterogeneity present in all five models, and the meta-regression analyses suggested that ethnic diversity might induce this heterogeneity (T vs. C: Adj R-squared=94.72%, P=0.01; CT vs. CC: Adj R-squared=94.18%, P=0.06; TT vs. CC: Adj R-squared=100%, P<0.01; CT+TT vs. CC: Adj R-squared=93.92%, P=0.03; TT vs. CC+CT: Adj R-squared=100%, P<0.01). The heterogeneity was relieved in the subsequent subgroup analysis.

Next, sensitivity analyses indicated that all results were consistent, without any qualitative change, through elimination of each study one by one (**Figure 3** for CT+TT vs. CC model). Publication bias analyses did not reveal any asymmetry (**Figure 4** for the CT+TT vs. CC model). This result was also supported by the Egger's test (T vs. C: P=0.15; CT vs. CC: P=0.17; TT vs. CC: P=0.23; CT+TT vs. CC: P=0.15; TT vs. CC+CT: P=0.84).

Meta-analysis results for rs4759314 A>G and rs1899663 G>T polymorphisms: Five selected studies, involving 3748 cases and 4509 controls, included in the analysis focused on the association between rs4759314 A>G and cancer risk. In order to assess the risk associated with rs1899663 G>T, two eligible studies involving 1,500 cases and 2,000 controls were included. Overall, no significant association was found in any of the models for the two SNPs (**Table 2**). The subgroup analyses according to ethnicity, control design, and genotyping methods did not reveal any significant associations either.

Discussion

Cancer is the most common malignant disease worldwide. Evidence suggests that the interactions between genetic mutation, living habits, environmental population, chronic inflammation, and virus infections might be important factors in tumorigenesis. To date, several studies have demonstrated that the abnormal expression of lncRNAs deregulate various biological procedures, including cancer development [28]. Gupta et al. [29] and Nakagawa et al. [30] reported significantly higher HOTAIR expression in breast cancer and non-small cell lung cancer compared with that observed in normal tissue, which enhanced aggressive cellular behavior and prompted metastasis.

Table 2. Summary ORs and 95% CI oflncRNA HOTAIR polymorphisms and cancer risk

Locus	N*	No. of case/ control	OR	95% CI	P	I^2 (%)[a]	OR	95% CI	*P*	I^2 (%)[a]	OR	95% CI	*P*	I^2 (%)[a]	OR	95% CI	*P*	I^2 (%)[a]	OR	95% CI	*P*	I^2 (%)[a]
rs920778 C>T				T vs. C				CT vs. CC				TT vs. CC				CT+TT vs. CC				TT vs. CC+CT		
Total	7	3123/4081	1.33	1.13-1.56	<0.01	75.0	1.24	1.03-1.49	0.02	63.5	2.03	1.25-3.30	<0.01	80.5	1.33	1.10-1.62	<0.01	70.4	1.97	1.34-2.90	<0.01	74.1
HWE	6	2623/3081	1.32	1.08-1.60	<0.01	78.7	1.23	0.99-1.55	0.07	67.9	1.90	1.07-3.37	0.03	83.3	1.33	1.04-1.68	0.02	74.0	1.88	1.21-2.90	<0.01	77.0
Ethnicity																						
Asian	5	2898/3750	1.47	1.35-1.59	<0.01	27.1	1.33	1.19-1.47	<0.01	2.1	2.89	2.30-3.64	<0.01	0	1.46	1.32-1.61	<0.01	24.2	2.58	2.06-3.32	<0.01	0
Caucasian	2	225/331	0.84	0.66-1.08	0.17	0	0.61	0.25-1.47	0.27	70.8	0.65	0.39-1.08	0.10	25.2	0.63	0.29-1.35	0.23	65.3	0.93	0.64-1.34	0.67	0
Design																						
PB	3	2098/2150	1.48	1.34-1.64	<0.01	21.1	1.34	1.18-1.52	<0.01	0	2.81	2.13-3.71	<0.01	2.2	1.48	1.31-1.67	<0.01	4.7	2.51	1.91-3.29	<0.01	0
HB	4	1025/1931	1.14	0.84-1.57	0.40	82.9	1.00	0.65-1.54	0.99	78.2	1.45	0.59-3.56	0.42	87.2	1.05	0.68-1.65	0.81	81.8	1.59	0.86-2.94	0.14	80.6
Genotyping																						
PCR-RFLP	5	2898/3750	1.47	1.35-1.59	<0.01	27.1	1.33	1.19-1.47	<0.01	2.1	2.89	2.30-3.64	<0.01	0	1.46	1.32-1.61	<0.01	24.2	2.58	2.06-3.32	<0.01	0
Taqman	2	225/331	0.84	0.66-1.08	0.17	0	0.61	0.25-1.47	0.27	70.8	0.65	0.39-1.08	0.10	25.2	0.63	0.29-1.35	0.23	65.3	0.93	0.64-1.34	0.67	0
rs4759314 A>G				G vs. A				AG vs. AA				GG vs. AA				AG+GG vs. AA				GG vs. AA+AG		
Total	5	3748/4509	0.94	0.82-1.07	0.34	0	0.95	0.82-1.10	0.50	0	0.66	0.29-1.50	0.32	30.2	0.94	0.82-1.09	0.41	0	0.66	0.29-1.50	0.33	30.0
Design																						
PB	3	2733/2855	0.88	0.75-1.03	0.12	0	0.89	0.75-1.06	0.20	0	0.80	0.11-5.82	0.83	64.6	0.88	0.75-1.05	0.15	0	0.81	0.11-5.87	0.84	64.5
HB	2	1015/1654	1.10	0.85-1.42	0.48	0	1.11	0.85-1.46	0.43	0	0.86	0.15-4.82	0.86	0	1.11	0.85-1.44	0.45	0	0.84	0.15-4.76	0.85	0
Genotyping																						
PCR-RFLP	3	2015/2654	1.02	0.84-1.24	0.81	0	1.02	0.83-1.25	0.85	0	1.15	0.30-4.47	0.84	0	1.02	0.84-1.25	0.83	0	1.15	0.30-4.45	0.84	0
RT-PCR	2	1733/1855	0.86	0.71-1.04	0.12	0	0.89	0.73-1.09	0.26	0	0.53	0.03-10.04	0.68	79.8	0.87	0.72-1.06	0.18	0	0.54	0.03-10.50	0.68	79.7
rs1899663 G>T				T vs. G				GT vs. GG				TT vs. GG				GT+TT vs. GG				TT vs. GG+GT		
Total	2	1500/2000	0.95	0.83-1.09	0.44	0	0.97	0.83-1.14	0.73	0	0.77	0.46-1.29	0.33	0	0.96	0.82-1.12	0.58	0	0.78	0.47-1.29	0.33	0

*Numbers of comparisons; [a]Test for heterogeneity; PB: Population-based; HB: Hospital-based; RT-PCR: Real-time PCR.

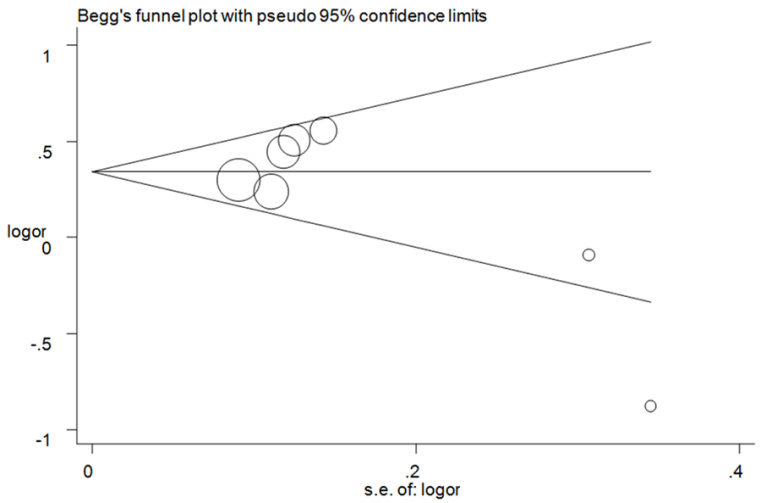

Figure 3. Funnel plot analysis to detect publication bias for CT+TT vs. CC model of lncRNAHOTAIRrs920778 C>T polymorphism. Circles represent the weight of the studies.

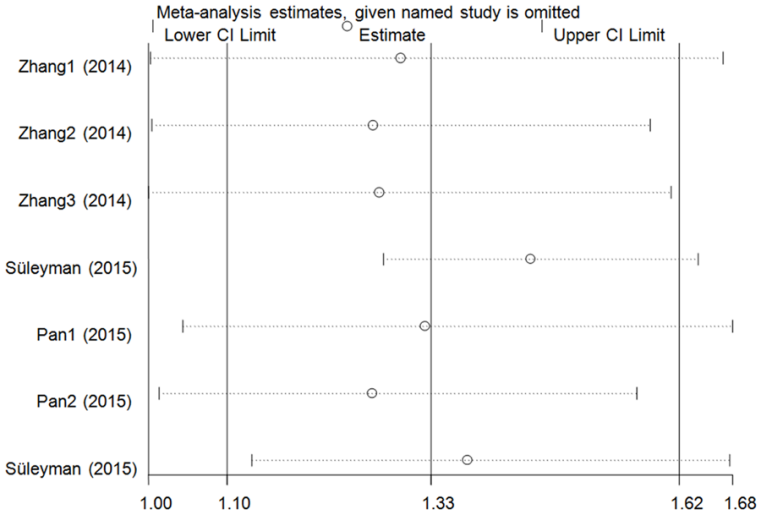

Figure 4. Sensitivity analysis via deletion of each individual study reflects the relative influence of each individual dataset on the pooled ORs in the CT+TT vs. CC model of lncRNAHOTAIRrs920778 C>T polymorphism and cancer risk.

Genomic mutations, particularly SNPs, are critical to the transformation from a normal cell to a cancerous cell, rendering it capable of rapid proliferation and metastasis. Since 2000, researchers have focused on polymorphisms that are located in non-coding regions of the genome, including those in microRNAs and lncRNAs. In this context, three important polymorphisms of HOTAIR (rs920778 C>T, rs4759314 A>G, rs1899663 G>T) were reported by several molecular epidemiological studies. For example, Zhang et al. [15] reported, for the first time, the association between HOTAIR polymorphisms and esophageal squamous cell carcinoma (ESCC) risk. They found that the homozygous TT mutation in rs920778 C>T induced significantly increased ESCC risk to Chinese populations, compared with its wild type homozygous CC counterpart. Since then, numerous similar studies were reported, but the conclusions have not been consistent.

In this meta-analysis, we explored the associations between the lncRNA HOTAIR (rs920778 C>T, rs4759314 A>G, rs1899663 G>T) polymorphisms and cancer risk in selected case-control studies. We observed significant associations of rs920778 C>T with cancer risk in Asian populations but not in Caucasian populations. Our meta-analysis indicates that ethnic diversity might be a basic factor in differential cancer susceptibility in different populations. In contrast, no significant associations were found with rs4759314 A>G and rs1899663 G>T.

To the best of our knowledge, this is the first meta-analysis to investigate the association between the lncRNA HOTAIR (rs920778 C>T, rs4759314 A>G, rs1899663 G>T) polymorphisms and cancer risk. Although heterogeneity was present for rs920778 C>T overall, the subgroup analyses successfully reduced heterogeneity in Asian populations. This also suggests that ethnic diversity might underlie this heterogeneity. Moreover, no publication bias existed for any of the three polymorphisms. All the five comparison models yielded consistent conclusions, which also indicate that our results are stable.

However, few limitations in this meta-analysis need to be addressed. First, only six eligible articles were selected that reported small sample sizes. The result might deviate from the real

association between lncRNA HOTAIR polymorphisms and cancer risk for insufficient data. Second, six studies included in our study were conducted in Chinese and Turkish populations. Therefore, potential ethnicity bias might exist owing to which our results might not be applicable to other races. Third, cancer could arise from multifactorial interactions between genetic mutations, environmental changes, lifestyle, diet, age, etc. These complex intrinsic mechanisms are beyond the scope of our meta-analysis of unadjusted databases.

Conclusions

Despite the above-mentioned limitations, this meta-analysis indicates that lncRNA HOTAIR rs920778 C>T polymorphism might be an increased risk factor for cancer development, especially in Asian populations. For complete elucidation, further studies associating lncRNA HOTAIR polymorphisms, environmental factors, and cancer risk are needed.

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Disclosure of conflict of interest

None.

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