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ORIGINAL RESEARCH

Significant association between long non-coding RNA HOTAIR polymorphisms and cancer susceptibility: a meta-analysis

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Abstract: HOTAIR, a well-known long non-coding RNA, is involved in carcinogenesis and progression of multiple cancers. Molecular epidemiological studies suggest that HOTAIR polymorphisms may be associated with cancer susceptibility, but the results remain controversial. To derive a more precise evaluation, we performed a meta-analysis focused on the associations between HOTAIR polymorphisms and cancer risk for the first time. PubMed, Embase, China National Knowledge Infrastructure, and Wanfang databases were searched. Odds ratios (ORs) with 95% confidence interval (CI) were applied to assess the association between HOTAIR rs920778 C>T, rs4759314 A>G, rs7958904 G>C, and rs1899663 G>T polymorphisms and cancer susceptibility. Analyses were conducted to detect heterogeneity, sensitivity, and publication bias in order to measure the robustness of our findings. Overall, 13 related studies involving 7,151 patients and 8,740 control samples were analyzed. Significant associations between the HOTAIR rs920778 polymorphism and cancer risk were observed (T vs C: OR =1.33, 95% CI =1.17–1.53; TT vs TC + CC: OR =1.55, 95% CI =1.21–2.00; TC + TT vs CC: OR =1.33, 95% CI =1.11–1.59; TT vs CC: OR =2.02, 95% CI =1.31–3.10) in the total population, as well as in subgroup analyses. For rs4759314 A>G polymorphism, a similarly increased risk was found in the gastric cancer group. However, significant decreases in cancer risk were observed both in the overall population and colorectal cancer group for rs7958904 G>C polymorphism. In addition, no significant association was detected between rs1899663 G>T polymorphism and cancer susceptibility. In conclusion, our meta-analyses suggest that HOTAIR polymorphisms may be associated with the risk of cancer development.

Keywords: HOTAIR, polymorphism, cancer susceptibility

Introduction

Cancer has now become one of the main causes of morbidity and mortality worldwide.[1] Overall, approximately 14.1 million new cases and 8.2 million deaths occurred in 2012, and most of them occurred in less developed countries.[2] Despite recent advances in treatment of surgery, chemotherapy, and radiotherapy, the 5-year survival rate remains low in many types of cancers.[3] Therefore, it is vital to identify the factors leading to cancer susceptibility. Nowadays, many molecular epidemiological studies have reported that genetic factors may play an important role in cancer development, and the genetic predisposition is receiving increasing attention.[4,5]

Long non-coding RNAs (lncRNAs) are defined as a new group of transcribed RNA molecules that are longer than 200 nucleotides and have no obvious protein-coding capacity.[6,7] LncRNAs were previously considered as a fake transcriptional noise,[8] but now accumulating evidence suggests that they are crucial players in a wide range of

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biological processes including cell proliferation, survival, metabolism, and differentiation.[9–11] Moreover, lncRNAs exhibit unique profiles in many types of cancers, contribute to carcinogenesis and progression, and are reasonably regarded as predictors of patient outcomes.[12–14]

HOTAIR, a prominently focused lncRNA, was initially identified to be implicated in breast cancer and promote tumor invasiveness and metastasis in 2007.[15] It has been reported that HOTAIR could interact with PRC2 and induce its relating methylation of H3K27 to reprogram chromatin organization.[15,16] Recently, the overexpression of HOTAIR and significant association with poor prognosis in a variety of human cancers including liver, breast, colon, lung, stomach, and esophageal cancers has been found.[17–21] All this convincing proof indicates the oncogenic role of HOTAIR in the course of several human carcinogenesis. Therefore, increasing studies have investigated the single nucleotide polymorphisms (SNPs) in the HOTAIR locus with cancer risk. However, the results were inconsistent and inconclusive. Thus, a comprehensive meta-analysis involving the related studies was performed to assess the possible association between HOTAIR polymorphisms and cancer susceptibility.

Material and methods

Search strategy

The PubMed, Embase, China National Knowledge Infrastructure, and Wanfang databases were searched to identify studies that examined the association between HOTAIR polymorphisms and cancer susceptibility prior to January 31, 2016. The following medical subject heading terms were used: (HOTAIR OR HOX transcript antisense RNA OR long noncoding RNA OR lncRNA OR lincRNA) AND (cancer OR carcinoma OR tumor OR neoplasia OR neoplasm) AND (polymorphism OR genotype OR allele OR variant OR SNP).

Eligibility criteria

All selected studies had to meet the following criteria: 1) published studies based on case-control design assessing the association between the HOTAIR polymorphisms and cancer susceptibility; 2) the study included sufficient genotype distribution data to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Studies were excluded if they investigated the progression, severity, phenotype modification, response to treatment, survival or family based studies. Moreover, meeting abstracts, case reports, editorials, and review articles were also excluded. For duplicate publications, the one with more complete design or larger sample size was finally selected.

Data extraction

Two independent researchers extracted the data from each relevant study including the first author, publication year, study country/region, ethnicity of participants (such as Asian or Caucasian), sources of controls, genotyping method, case-control matched status, type of cancers, Hardy-Weinberg equilibrium (HWE) status of controls, and number of genotypes in cancer cases and controls. Disagreements were reconciled through group discussion. The HWE was calculated based on the genotypes of the controls.

Statistical analysis

ORs with 95% CIs were used to assess the strength of the association between the HOTAIR polymorphisms and cancer risk. For the HOTAIR rs920778 C>T polymorphism, the pooled ORs were obtained for allele (T vs C), recessive (TT vs TC + CC), dominant (TC + TT vs CC), and homozygous (co-dominant) model (TT vs CC). Similar genetic models were also assessed for HOTAIR rs4759314 A>G, rs7958904 G>C, and rs1899663 G>T variants. Subgroup analyses were performed based on ethnicity, source of controls, genotyping methods, type of cancers, case-control matched status, and HWE status of controls. ORs were calculated using the random-effect model when the I^2 was greater than 50%. Otherwise, a fixed-effect model was adopted. In order to evaluate the stability of the results, sensitivity analysis was used, which meant omitting one study at a time, and then compared to show whether a significant difference existed between the former and the latter results. Publication bias was examined by the visual inspection of funnel plot, and Egger's regression test. Data were analyzed and processed using Stata 12.0 (StataCorp LP, College Station, TX, USA). $P<0.05$ was considered statistically significant.

Results

Study characteristics

A systematic search of the literature identified 135 relevant studies. The study selection process is shown in Figure 1. Following the selection criteria, 127 studies were excluded from our research due to various deficiencies. Ultimately, eight eligible articles were selected with adequate data, including eight studies on rs920778 C>T,[22–26] eight studies on rs4759314 A>G,[24–29] three publications on rs1899663 G>T,[24–26] and three studies on rs7958904 G>C,[28,29] respectively. All studies were published between 2014 and 2016. Only two studies involved Caucasian populations, and other studies involved Asian populations. The genotype distribution was in agreement with HWE in all studies except for one study

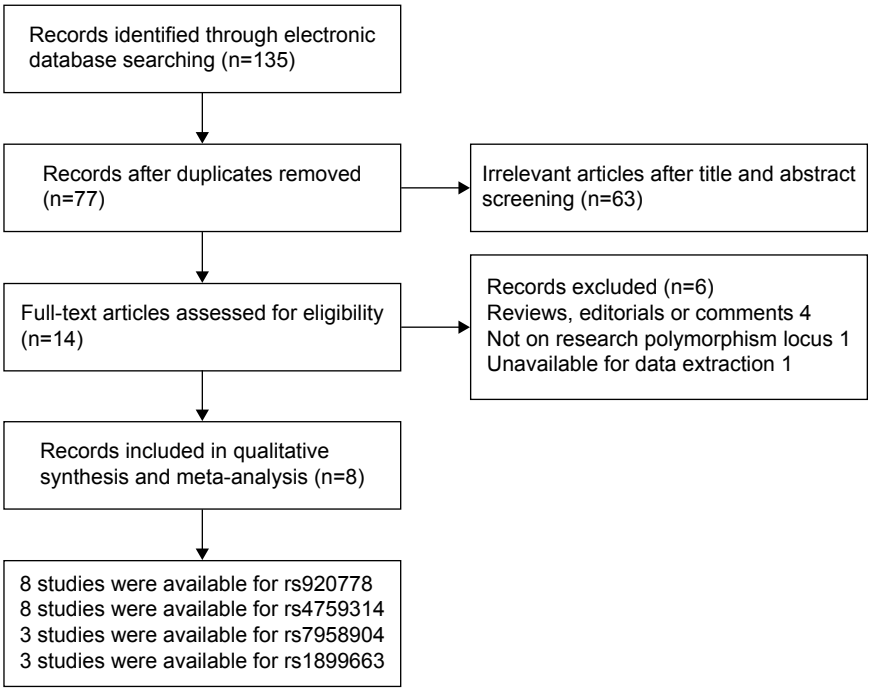

Figure 1 Flow diagram of the study selection process.

of HOTAIR rs920778 C>T polymorphism. Detailed characteristics of studies included are summarized in Table 1.

Association between the HOTAIR rs920778 C>T polymorphism and cancer risk

A total of eight relevant studies, consisting of 3,627 patients and 4,585 controls, were examined for the association between the HOTAIR rs920778 C>T polymorphism and cancer risk. The combined analyses revealed a significantly increased risk of cancer for this polymorphism in all four genetic models (T vs C: OR =1.33, 95% CI =1.17–1.53, $P<0.01$, I^2=68.1%; TT vs TC + CC: OR =1.55, 95% CI =1.21–2.00, P=0.001, I^2=59.7%; TC + TT vs CC: OR =1.33, 95% CI =1.11–1.59, P=0.002, I^2=63.6%; TT vs CC: OR =2.01, 95% CI =1.31–3.10, P=0.001, I^2=77.0%; Figure 2, Table 2). Subsequent analyses accounting for ethnicity revealed similar results in Asian populations, using all four genotype models. Significant correlations with increased cancer risk were also observed in the population-based control group and studies restricted to HWE. Enhanced cancer risk was also observed in the subgroup analysis with genotyping method of restriction fragment length polymorphism under all four genetic models. Moreover, elevated risks of gastric cancer (T vs C: OR =1.32, 95% CI =1.01–1.72, P=0.045, I^2=73.8%; TC + TT vs CC: OR =1.36, 95% CI =1.02–1.83, P=0.039, I^2=59.0%; TT vs CC: OR =2.12, 95% CI =1.00–4.51, P=0.050, I^2=78.1%) and esophageal cancer (T vs C: OR =1.46, 95% CI =1.32–1.61, $P<0.001$, I^2=0; TT vs TC + CC: OR =1.96, 95% CI =1.48–2.59, $P<0.001$, I^2=59.7%; TC + TT vs CC: OR =1.44, 95% CI =1.27–1.62, $P<0.001$, I^2=0; TT vs CC: OR =2.81, 95% CI =2.13–3.71, $P<0.001$, I^2=2.2%; Table 2) were detected.

Sensitivity analysis showed that no single study qualitatively changed the pooled ORs with corresponding 95% CI, indicating that the results of this meta-analysis were highly stable (see Figure 3 for allele contrast model). Visual inspection of funnel plot did not reveal any asymmetrical evidence (see Figure 4 for allele contrast model). The results were further supported by the analysis of the data with Egger's test (T vs C: P=0.121; TT vs TC + CC: P=0.062; TC + TT vs CC: P=0.243; TT vs CC: P=0.195).

Association between HOTAIR rs4759314 A>G polymorphism and cancer risk

Eight studies consisting of 5,526 cases and 6,659 controls were included in the analysis to determine whether the HOTAIR rs4759314 A>G polymorphism was associated with cancer risk. Overall, no significant association was observed in all four models (Table 2). Only two genetic models (for G vs A, OR =1.29, 95% CI =1.10–1.51, P=0.002, I^2=43.5%; for GA + GG vs AA, OR =1.32, 95% CI =1.12–1.56,

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

Reference	Year	Country/region	Ethnicity	Source of controls	Case	Control	Genotype distribution						Genotyping methods	Age- and sex-matched	Type of cancer	*P* for HWE[a]
							Case			Control						
rs920778 C>T							**TT**	**TC**	**CC**	**TT**	**TC**	**CC**				
Pan et al[25]	2016	People's Republic of China	Asian	Population	500	1,000	31	194	275	24	368	608	RFLP	Matched	Gastric cancer	0.000
Pan et al[25]	2016	People's Republic of China	Asian	Population	300	600	28	127	145	21	207	372	RFLP	Matched	Gastric cancer	0.230
Bayram et al[22]	2015	Turkey	Caucasian	Hospital	104	209	32	52	20	66	105	38	Taqman	Matched	Gastric cancer	0.738
Bayram et al[23]	2015	Turkey	Caucasian	Hospital	123	122	40	52	31	41	66	15	Taqman	Matched	Breast cancer	0.140
Yan et al[24]	2015	People's Republic of China	Asian	Population	502	504	339	151	12	296	190	18	RFLP	Matched	Breast cancer	0.748
Zhang et al[26]	2014	People's Republic of China	Asian	Population	1,000	1,000	83	389	528	41	358	601	RFLP	Matched	Esophageal cancer	0.173
Zhang et al[26]	2014	People's Republic of China	Asian	Hospital	510	550	47	207	256	20	186	344	RFLP	Matched	Esophageal cancer	0.401
Zhang et al[26]	2014	People's Republic of China	Asian	Population	588	600	51	203	307	17	205	378	RFLP	Matched	Esophageal cancer	0.082
rs4759314 A>G							**GG**	**GA**	**AA**	**GG**	**GA**	**AA**				
Pan et al[25]	2016	People's Republic of China	Asian	Population	500	1,000	1	48	451	3	83	914	RFLP	Matched	Gastric cancer	0.448
Du et al[28]	2015	People's Republic of China	Asian	Hospital	753	1,057	3	126	624	6	136	915	Taqman	Matched	Gastric cancer	0.699
Du et al[28]	2015	People's Republic of China	Asian	Hospital	522	589	3	60	459	2	36	549	Taqman	Matched	Gastric cancer	0.098
Yan et al[24]	2015	People's Republic of China	Asian	Population	502	504	1	50	451	2	54	448	RFLP	Matched	Breast cancer	0.785
Guo et al[27]	2015	People's Republic of China	Asian	Population	515	654	1	53	461	1	64	589	RFLP	Unmatched	Gastric cancer	0.587
Xue et al[29]	2015	People's Republic of China	Asian	Hospital	1,147	1,203	1	135	1,011	9	157	1,037	Taqman	Matched	Colorectal cancer	0.260
Xue et al[29]	2015	People's Republic of China	Asian	Hospital	587	652	4	65	517	2	79	571	Taqman	Matched	Colorectal cancer	0.673
Zhang et al[26]	2014	People's Republic of China	Asian	Population	1,000	1,000	2	81	917	1	89	910	RFLP	Matched	Esophageal cancer	0.436
rs7958904 G>C							**CC**	**CG**	**GG**	**CC**	**CG**	**GG**				
Du et al[28]	2015	People's Republic of China	Asian	Hospital	753	1,057	51	276	412	85	404	568	Taqman	Matched	Gastric cancer	0.271
Xue et al[29]	2015	People's Republic of China	Asian	Hospital	1,147	1,203	74	399	672	99	456	646	Taqman	Matched	Colorectal	0.147
Xue et al[29]	2015	People's Republic of China	Asian	Hospital	587	652	33	206	347	57	248	346	Taqman	Matched	Colorectal	0.192
rs1899663 G>T							**TT**	**TG**	**GG**	**TT**	**TG**	**GG**				
Pan et al[25]	2016	People's Republic of China	Asian	Population	500	1,000	6	118	376	13	255	732	RFLP	Matched	Gastric cancer	0.078
Yan et al[24]	2015	People's Republic of China	Asian	Population	502	504	14	149	339	20	158	326	RFLP	Matched	Breast cancer	0.876
Zhang et al[26]	2014	People's Republic of China	Asian	Population	1,000	1,000	19	256	725	26	250	724	RFLP	Matched	Esophageal cancer	0.430

Note: [a]HWE in control.

Abbreviations: HWE, Hardy-Weinberg equilibrium; RFLP, restriction fragment length polymorphism.

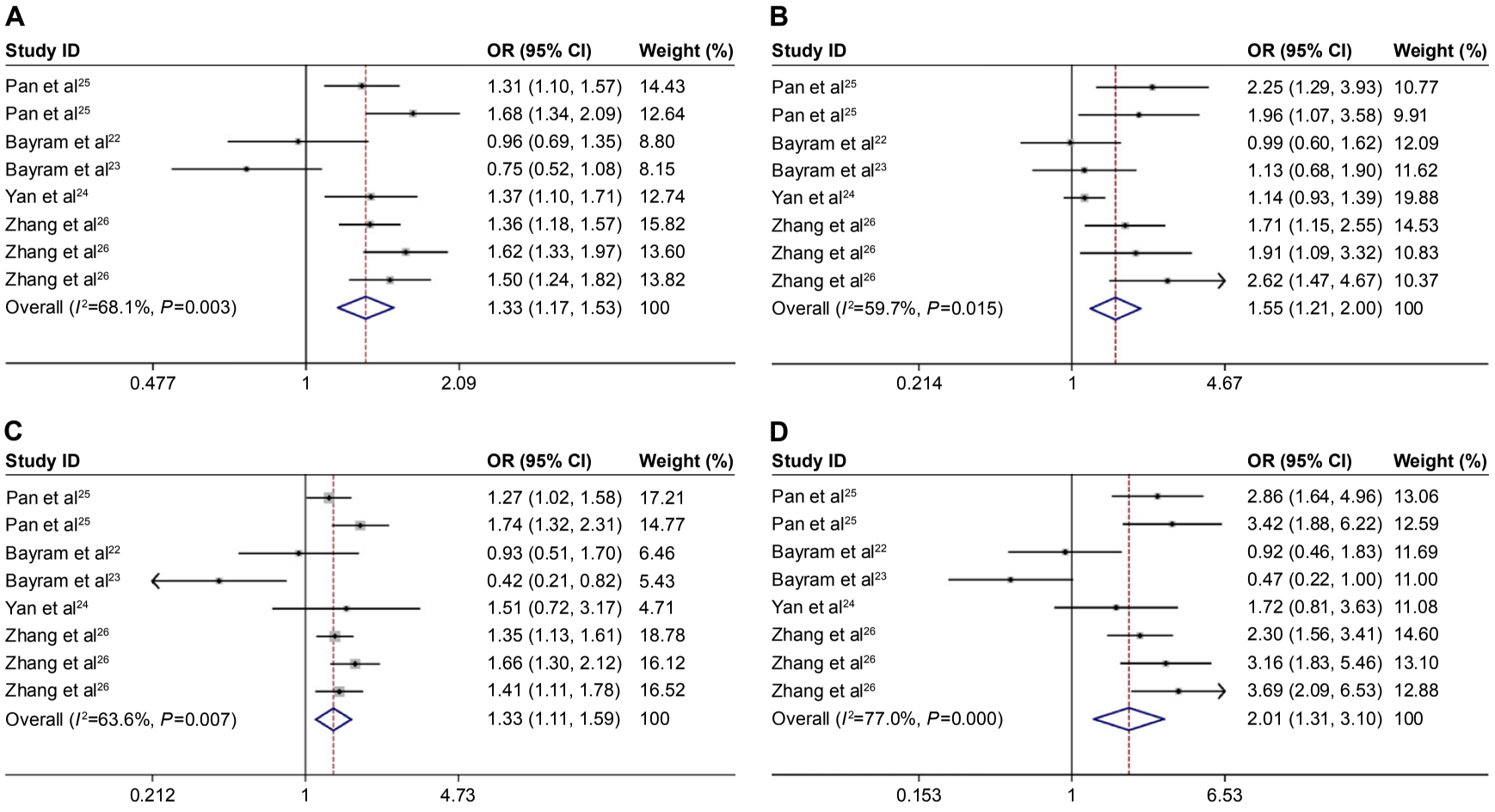

Figure 2 Calculated OR and 95% CIs for the associations between HOTAIR rs920778 polymorphism and cancer risk in overall populations.

Notes: (**A**) The allele contrast model; (**B**) the recessive model; (**C**) the dominant model; (**D**) the homozygous (co-dominant) model. The area of each square indicates the weight of the study in the meta-analysis. Weights are from random effect analysis.

Abbreviations: OR, odds ratio; CIs, confidence intervals.

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

Locus	N*	Number of case/control	Allele				Recessive				Dominant				Homozygote			
			OR	95% CI	*P*-value	I^2 (%)[a]	OR	95% CI	*P*-value	I^2 (%)[a]	OR	95% CI	*P*-value	I^2 (%)[a]	OR	95% CI	*P*-value	I^2 (%)[a]
rs920778																		
Total	8	3,627/4,585	1.33	1.17–1.53	<0.001	68.1	1.55	1.21–2.00	0.001	59.7	1.33	1.11–1.59	0.002	63.6	2.01	1.31–3.10	0.001	77.0
Ethnicity																		
Asian	6	3,400/4,254	1.44	1.34–1.56	<0.001	2.9	1.77	1.30–2.41	<0.001	66.0	1.44	1.30–1.58	<0.001	0	2.77	2.22–3.44	<0.001	0
Caucasian	2	227/331	0.86	0.67–1.10	0.218	0	1.06	0.74–1.51	0.768	0	0.63	0.29–1.40	0.257	67.4	0.68	0.41–1.12	0.129	39.4
Source of controls																		
Population	5	2,890/3,704	1.42	1.30–1.54	<0.001	0	1.76	1.23–2.51	0.002	70.8	1.40	1.25–1.56	<0.001	0	2.70	2.12–3.42	<0.001	0
Hospital	3	737/881	1.07	0.66–1.75	0.778	87.9	1.27	0.94–1.70	0.118	38.1	0.90	0.40–2.03	0.808	87.3	1.14	0.37–3.55	0.825	88.8
Method																		
Taqman	2	227/331	0.86	0.67–1.10	0.218	0	1.06	0.74–1.51	0.768	0	0.63	0.29–1.40	0.257	67.4	0.68	0.41–1.12	0.129	39.4
RFLP	6	3,400/4,254	1.44	1.34–1.56	<0.001	2.9	1.77	1.30–2.41	<0.001	66.0	1.44	1.30–1.58	<0.001	0	2.77	2.22–3.44	<0.001	0
Type of cancer																		
Gastric cancer	3	904/1,809	1.32	1.01–1.72	0.045	73.8	1.61	0.95–2.72	0.078	63.5	1.36	1.02–1.83	0.039	59.0	2.12	1.00–4.51	0.050	78.1
Breast cancer	2	625/626	1.03	0.57–1.86	0.917	87.2	1.14	0.94–1.37	0.181	0	0.79	0.22–2.78	0.709	84.3	0.90	0.25–3.20	0.873	82.4
Esophageal cancer	3	2,098/2,150	1.46	1.32–1.61	<0.001	0.8	1.96	1.48–2.59	<0.001	0	1.44	1.27–1.62	<0.001	0	2.81	2.13–3.71	<0.001	2.2
Controls in HWE	7	3,127/3,585	1.33	1.14–1.56	<0.001	72.2	1.48	1.14–1.92	0.003	57.8	1.32	1.06–1.65	0.012	67.6	1.90	1.16–3.12	0.011	79.7
rs4759314																		
Total	8	5,526/6,659	1.07	0.90–1.28	0.461	59.9	0.68	0.36–1.29	0.233	0	1.08	0.90–1.30	0.401	59.1	0.75	0.40–1.40	0.366	0
Source of controls																		
Population	4	2,517/3,158	1.00	0.84–1.19	0.962	0	0.93	0.29–3.00	0.898	0	1.00	0.83–1.20	0.977	0	0.93	0.29–2.99	0.901	0
Hospital	4	3,009/3,501	1.15	0.83–1.61	0.403	81.1	0.59	0.28–1.28	0.184	34.6	1.18	0.83–1.66	0.356	80.2	0.69	0.33–1.45	0.325	48.4
Method																		
Taqman	4	3,009/3,501	1.15	0.83–1.61	0.403	81.1	0.59	0.28–1.28	0.184	34.6	1.18	0.83–1.66	0.356	80.2	0.69	0.33–1.45	0.325	48.4
PCR-RFLP	4	2,517/3,158	1.00	0.84–1.19	0.962	0	0.93	0.29–3.00	0.898	0	1.00	0.83–1.20	0.977	0	0.93	0.29–2.99	0.901	0
Type of cancer																		
Gastric cancer	4	2,290/3,300	1.29	1.10–1.51	0.002	43.5	0.69	0.27–1.74	0.430	0	1.32	1.12–1.56	0.001	44.0	0.97	0.39–2.41	0.954	0
Breast cancer	1	502/504	0.90	0.61–1.32	0.571	NA	0.55	0.05–6.24	0.629	NA	0.91	0.61–1.35	0.625	NA	0.50	0.05–5.50	0.568	NA
Colorectal cancer	2	1,734/1,855	0.86	0.71–1.04	0.123	0	0.60	0.03–10.39	0.724	77.6	0.87	0.72–1.06	0.177	0	0.53	0.03–10.40	0.677	79.8
Esophageal cancer	1	1,000/1,000	0.93	0.69–1.26	0.644	NA	2.17	0.19–24.36	0.531	NA	0.92	0.67–1.25	0.578	NA	1.99	0.18–21.93	0.576	NA
Age- and sex-matched	7	5,011/6,005	1.07	0.88–1.31	0.497	65.7	0.66	0.34–1.27	0.210	0	1.09	0.88–1.34	0.434	65.0	0.73	0.38–1.39	0.335	7.2
rs7958904																		
Total	3	2,487/2,912	0.85	0.78–0.93	<0.001	0	0.85	0.69–1.06	0.143	0	0.84	0.76–0.94	0.002	0	0.72	0.58–0.89	0.002	0
Type of cancer																		
Gastric cancer	1	753/1,057	0.92	0.79–1.07	0.292	NA	0.90	0.62–1.31	0.570	NA	0.92	0.76–1.11	0.399	NA	0.83	0.57–1.20	0.314	NA
Colorectal cancer	2	1,734/1,855	0.82	0.74–0.91	<0.001	0	0.83	0.64–1.08	0.163	0	0.81	0.71–0.92	0.001	0	0.67	0.51–0.87	0.002	0
rs1899663																		
Total	3	2,002/2,504	0.93	0.83–1.04	0.208	0	0.79	0.52–1.20	0.265	0	0.94	0.82–1.07	0.334	0	0.74	0.49–1.11	0.147	0

Notes: *Numbers of comparisons. [a]Test for heterogeneity. *P*-values were obtained from *Z*-test.

Abbreviations: RFLP, restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium; NA, not available; ORs, odds ratios; CI, confidence interval; PCR, polymerase chain reaction.

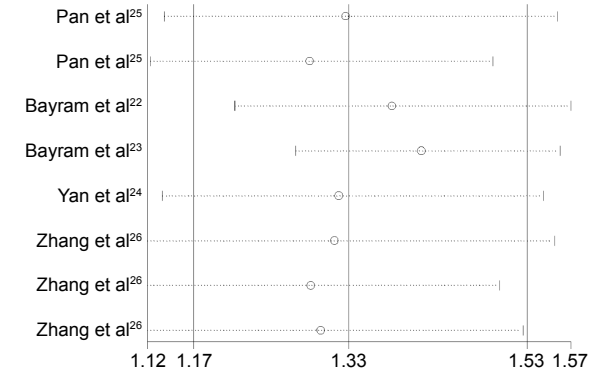

Figure 3 Sensitivity analysis via deletion of each individual study reflects the relative influence of each individual dataset on the pooled ORs in the allele contrast model of HOTAIR rs920778 polymorphism.
Abbreviation: ORs, odds ratios.

P=0.001, I^2=44.0%) revealed increased risk in the gastric cancer group. Further subgroup analyses of genotyping method, source of controls, and case-control matched status were conducted, and no significant association was identified (Table 2). The pooled ORs did not exhibit any change with sensitivity analysis, and no publication bias was observed (G vs A: *P*=0.350; GG vs GA + AA: *P*=0.902; GA + GG vs AA: *P*=0.408; GG vs AA: *P*=0.823).

Association between HOTAIR rs7958904 G>C polymorphism and cancer risk

Three eligible studies including 2,487 cases and 2,912 controls focused on the association of HOTAIR rs7958904 G>C polymorphism with cancer. The heterogeneity among studies, measured by I^2 statistic, was not significant in all genetic models (I^2<0.5). Therefore, the fixed effect model was used in all genetic models. A significant decrease in cancer risk was observed in the overall population (C vs G: OR =0.85, 95% CI =0.78–0.93, *P*<0.001, I^2=0%; CG + CC vs GG: OR =0.84, 95% CI =0.76–0.94, *P*=0.002, I^2=0; CC vs GG: OR =0.72, 95% CI =0.58–0.89, *P*=0.002, I^2=0; Table 2). Moreover, these results were consistent with subgroup analysis of the colorectal cancer group (Table 2). Sensitivity analysis was conducted, and no conspicuous change of the pooled ORs was detected. No publication bias was observed, indicating that the results are statistically robust (C vs G: *P*=0.757; CC vs CG + GG: *P*=0.354; CG + CC vs GG: *P*=0.870; CC vs GG: *P*=0.587).

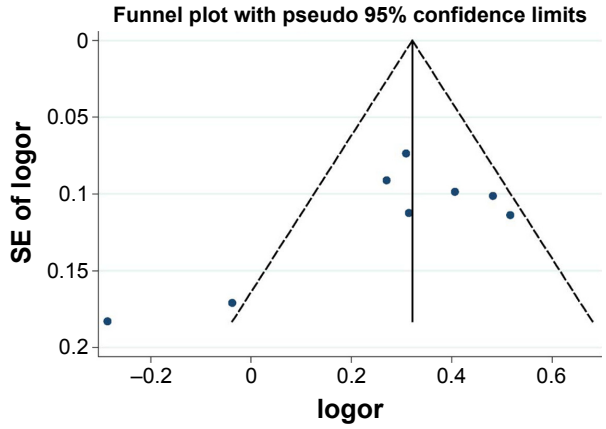

Figure 4 Funnel plot analysis to detect publication bias for the allele contrast model of HOTAIR rs920778 polymorphism.
Abbreviation: SE, standard error.

Association between the HOTAIR rs1899663 G>T polymorphism and cancer risk

Three studies with 2,002 cases and 2,504 controls were included in the HOTAIR rs1899663 G>T polymorphism and cancer risk research. No significant associations were found in all four models for this SNP locus (Table 2).

Discussion

Genetic variants, mainly composed of SNPs, have been shown to influence the susceptibility of patients to cancer and have attracted increasing attention. LncRNAs play crucial roles in a wide range of biological processes and are involved in the development and progression of multiple cancers. SNPs in several lncRNAs previously identified to be involved in carcinogenesis have been reported to be associated with cancer risk.[30,31]

Recently, several molecular epidemiological studies have been conducted to evaluate the association between polymorphisms of HOTAIR and the risk of cancer development, but results have remained conflicting. Regarding the HOTAIR rs920778 C>T polymorphism, Pan et al reported that the TT carriers had a 1.66- and 1.87-fold increased gastric cancer risk in Jinan and Huaian populations of People's Republic of China compared with the CC carriers.[25] A similar increase in esophageal cancer risk was also observed in three independent case-control sets consisting of 4,248 Chinese subjects.[26] However, CC genotype of HOTAIR rs920778 polymorphism was found to significantly increase the risk of breast cancer in a Turkish population, whereas another study demonstrated that the HOTAIR rs920778 polymorphism had not played any major role in genetic susceptibility to gastric carcinogenesis.[22,23]

To our knowledge, this is the first meta-analysis to date focused on the association between polymorphisms in

lncRNA HOTAIR and cancer susceptibility specially. All the relative studies about cancer risk and four polymorphisms of HOTAIR were collected to make a precise conclusion. Overall, significant increased risk of cancer was observed for the HOTAIR rs920778 C>T polymorphism. In subgroup analyses by ethnicity, we found that individuals with the T allele and mutated genotypes had a significant increased cancer risk in Asian populations, suggesting that the increased cancer risk may be ethno-specific. Furthermore, it is worth noting that some significantly increased risks were observed in gastric and esophageal cancer, but not the breast cancer group. Similarly, the result that rs4759314 A>G polymorphism just increased the risk of gastric cancer rather than other types of cancers was revealed in our meta-analysis. While significant decreases in cancer risk were observed both in overall population and colorectal cancer group, indicating that rs7958904 G>C polymorphism might be a protective factor especially for colorectal cancer. In addition, a negative correlation was observed in the rs1899663 G>T polymorphism analysis.

Although the number of the included studies was relatively small, we believe that the findings can help to explain the association. First, in the sensitivity analysis, no significant changes were found after omitting each study at a time, indicating the relative stability and credibility of the results. Second, the genotype distributions in the controls of four selected SNP loci were all mostly consistent with HWE except for one study in rs920778 polymorphism analysis. Third, the visual inspection of funnel plot and Egger's test proved that almost no apparent publication bias existed in our meta-analysis. All these would guarantee the reliability of results.

However, it is important to note the limitations of our meta-analysis. First, heterogeneity across studies existed for rs920778 and rs4759314 polymorphisms. Unfortunately, we did not perform meta-regression analysis which is not suitable for assessing heterogeneity with a sample size less than ten.[32] Considering that ethnic diversity, study design difference, and measurement error may contribute to common sources of heterogeneity,[33] we performed subgroup analyses to explore the source of heterogeneity. For rs920778, the results of subgroup analyses did not effectively eliminate the heterogeneity, indicating that all above factors should be taken into consideration. Nevertheless, subgroup analyses were successfully used to relieve moderate heterogeneity bias in the rs4759314 polymorphism analysis within the population-based control group and the genotyping method of restriction fragment length polymorphism group, suggesting that control sources and genotyping method may influence heterogeneity. The second limitation lies in the ethnicity of the subjects. Most of the patients were Asians in the present study and this limited the general application of the results to other populations. Third, all of our results may be influenced by casualness due to the small number of studies included and the limited sample size of each study. Finally, cancer is a multi-factorial malignant disease that likely arises from complex interactions between genetic mutations, environmental changes, lifestyle, diet, age, and sex. In our meta-analysis, we only focused on the HOTAIR polymorphisms, while the fundamental underlying mechanisms cannot be explained clearly due to unadjusted databases.

Conclusion

In conclusion, the current meta-analysis indicated that three functional polymorphisms of HOTAIR rs920778 C>T, rs4759314 A>G, and rs7958904 G>C may play an important role in the development of cancer. Given the limitations in the present meta-analysis, the results need to be interpreted with caution. Large-scale, case-control studies with rigorous designs should be conducted to confirm the association of above functional polymorphisms in lncRNA HOTAIR and cancer risk in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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