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ORIGINAL RESEARCH

The association between HOTAIR polymorphisms and cancer susceptibility: an updated systemic review and meta-analysis

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Objectives: This work aims to explore whether HOX transcript antisense intergenic RNA (HOTAIR) polymorphisms are associated with cancer susceptibility.

Materials and methods: A comprehensive search was conducted for literature published from January 2007 to July 2017. The pooled odds ratios (ORs) and the corresponding 95% CIs were calculated using the Revman 5.2 software. Eighteen articles of 36 case–control studies were enrolled including six HOTAIR polymorphisms and 10 cancer types.

Results: The results showed that cancer risk was elevated in recessive mutation of rs12826786 (TT vs CC+CT: OR =1.55, 95% CI =1.19, 2.03; TT+CT vs CC: OR =1.23, 95% CI =1.04, 1.46; TT vs CC: OR =1.67, 95% CI =1.24, 2.24; T vs C: OR =1.24, 95% CI =1.09, 1.40) and rs920778 (TT vs CC+CT: OR =1.73, 95% CI =1.30, 2.30; TT+CT vs CC: OR =1.40, 95% CI =1.16, 1.70; TT vs CC: OR =1.83, 95% CI =1.25, 2.68; T vs C: OR =1.37, 95% CI =1.18, 1.59), while the results for polymorphisms of rs7958904, rs4759314, rs874945, and rs1899663 were insignificant. The stratified results for Chinese population were consistent with the overall group analysis.

Conclusion: Our meta-analysis showed that HOTAIR polymorphisms of rs12826786 and rs920778 were correlated with increased cancer risk, while rs7958904, rs4759314, rs874945, and rs1899663 were not. More studies with different types of cancer are needed to confirm the findings.

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

Introduction

The recent sequencing technologies and genome-wide analysis have indicated that only 2% of the genome is in protein-encoded regions and that the majority of the genome is the so-called dark matter that is transcribed into noncoding RNAs (ncRNAs).[1–3] These ncRNAs are classified as short and long ncRNAs depending on the nucleotide size. Long ncRNAs (lncRNAs) are commonly defined as non-protein-coding transcripts longer than 200 nucleotides.[4,5] They are crucial players in a wide range of biologic processes on the epigenetic, transcriptional, or posttranscriptional level, and are the important regulators of pathophysiological activities such as cell growth, invasion, apoptosis, and metastasis.[6–8] So far, more than 3000 lncRNAs have been found, among which the HOX transcript antisense intergenic RNA (HOTAIR) is the mostly widely studied. HOTAIR is a 2.2 kb lncRNA that is transcribed in antisense orientation from the homebox C (HOXC) gene on chromosome 12q13.13. HOTAIR 5′-domain recruits the Polycomb Repressive Complex 2, leading to histone H3 lysine 27 trimethylation (H3K27me3) in the HOXD locus, and HOTAIR 3′-domain interacts with LSD1/REST/CoREST complex, to regulate the metastasis suppressor genes silence.[9,10] Clinical and biochemical studies have indicated that deregulation of HOTAIR is a powerful

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indicator of poor prognosis and malignant progression for several cancers such as ovarian cancer, gastric cancer, and lung cancer.[11–13]

Genetic variants, mainly composed of single-nucleotide polymorphisms (SNPs), have long been confirmed in various loci of the genome. These variants may exert various influences on the expression or function of a particular gene.[14,15] Even with the potential importance of HOTAIR in carcinogenesis, only a few studies have investigated the effects of HOTAIR SNPs on cancer susceptibility. For example, Guo et al reported that the mutated T allele of rs12826786 in HOTAIR could increase the risk of developing gastric cancer and was associated with TNM stage. In addition, higher expression levels of HOTAIR were found in tumor tissues, and rs12826786 SNP had a genotype-specific effect on HOTAIR expression.[16] However, in another case–control study conducted by Ulger et al, HOTAIR rs12826786 (C/T) polymorphism was not playing any major role in genetic susceptibility to gastric carcinogenesis in Turkish population.[17] As for HOTAIR rs7958904 (G/C), Jin et al found that the rs7958904 CC genotype was related to an increased risk of cervical cancer compared with the GG/GC genotypes. Their MTT assay demonstrated a growth-promoting role of rs7958904 C allele on cervical cancer cells.[18] On the contrary, Xue et al revealed that individuals with rs7958904 CC genotype had a significantly decreased risk of colorectal cancer in both stages 1 and 2, compared with those carrying GG genotype.[19]

To address the inconsistency among different case–control studies, some meta-analyses have been performed to draw a conclusion between HOTAIR polymorphisms and cancer susceptibility. Chu et al pooled eight articles on three HOTAIR polymorphisms and concluded that HOTAIR rs920778 increased the cancer risk in the recessive model.[20] Meanwhile, Lv et al summarized five HOTAIR polymorphisms from 16 studies, showing that the rs920778 (C/T) polymorphism was associated with increased risk of overall cancer in the recessive model, while the rs7958904 (G/C) polymorphism was associated with decreased overall risk of cancer in all genetic models.[21] Since then, several new case–control studies have been published, some of which reported controversial results compared with previous publications. Moreover, more types of polymorphisms have been explored, providing a perspective to a further systemic review. In this study, we comprehensively collected and assessed all the available articles using meta-analysis with the aim to better clarify the association between currently reported HOTAIR polymorphisms and cancer susceptibility.

Materials and methods

Search for eligible literature

A comprehensive electronic search was performed using PubMed, Embase, Medline (Ovid), Weipu, Wanfang, and CNKI for studies published from January 2007 to July 2017. The following keywords were variably combined: "cancer", "malignancy", "HOTAIR", "lncRNA", "polymorphism", "variant", and "mutation". The search was updated every week until July 15, 2017.

Inclusion and exclusion criteria

Articles fulfilling the following criteria were included: 1) analyzed HOTAIR polymorphisms in cancer; 2) provided sufficient data in both case and control groups to calculate the odds ratios (ORs) and the corresponding 95% CIs; 3) studied the polymorphisms that appeared in at least two publications; and 4) case–control studies. When duplicate data were present in different articles, only the latest one would be included. Meanwhile, articles that did not fulfill the criteria mentioned above were excluded.

Data extraction

Two investigators independently reviewed all potential studies. The following items were extracted: first author, year of publication, ethnicity, SNPs, cancer type, source of control, genotyping method, adjusted risk factors, and genotype distributions in cases and controls. Any discrepancies were resolved by discussion with a third investigator until a consensus was reached.

The Newcastle–Ottawa Scale (NOS) was used to investigate the quality of included studies. Three aspects of selection, comparability, and exposure (nine scores in total) were carefully evaluated. Studies with scores higher than 5 were included (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).[49]

Statistical analysis

Pooled ORs and corresponding 95% CIs were calculated to estimate the strength of the association between different HOTAIR SNPs and cancer risk. All SNPs were considered as binary variables, and five comparative models were used as follows: recessive genotype vs heterozygous genotype + dominant wild type, recessive genotype + heterozygous genotype vs dominant wild type, heterozygous genotype vs dominant wild type + recessive genotype, recessive genotype vs dominant wild type, and mutant allele vs wild-type allele. The *Z*-test was conducted to determine the significance of the pooled ORs where $P<0.05$ was interpreted as

statistically significant. Higgins I^2 test was used to assess heterogeneity among studies. When I^2 was <50%, a fixed-effects model was used, indicating the lack of heterogeneity; otherwise, a random-effects model was applied. The presence of publication bias was evaluated by the inspection of funnel plots. When the funnel plots showed visible asymmetry, Egger's test was performed to further measure the bias, which was considered as existing when $P<0.05$. All analyses were undertaken using Revman 5.2 software (Cochrane Collaboration, Copenhagen, Denmark) with the exception of the Egger's test, which was performed using STATA 14.0 (StataCorp LP, College Station, TX, USA).

Results

Search results

The initial search yielded 337 publications, 262 of which were excluded for being irrelevant to HOTAIR polymorphisms, by reading titles and abstracts. On further evaluation, 37 articles were either biochemical studies or reviews and were therefore ruled out; 18 articles focused on non-cancer diseases such as rheumatoid arthritis and hearing loss; 1 article explored the relationship between cervical cancer risk and HOTAIR rs2366152 polymorphisms, which were not repeated in other published studies, resulting in the impossibility of data pooling;[22] and 1 article focused on the HOTAIR rs7958904 polymorphisms in lung cancer, but failed to offer detailed genotype information data.[23] Therefore, we enrolled 18 articles of 36 studies in this meta-analysis (Figure 1).[16–19,24–37]

Study characteristics

Among the 36 enrolled case–control studies, six HOTAIR polymorphisms were analyzed (rs7958904, rs4759314, rs874945, rs12826786, rs1899663, and rs920778), while 10 cancer types were reported (breast cancer, cervical cancer, colorectal cancer, esophageal cancer, gastric cancer, glioma, lung cancer, ovarian cancer, prostate cancer, and thyroid cancer). Twelve articles were about Chinese population, four were about Turkish, one was about Iranian, and one was about Portuguese. The source of control was also retrieved. Despite the fact that there were 4 articles that failed to mention the detailed control source, 11 articles were hospital based and 3 were population based. The NOS showed that 14 articles were of moderate quality (NOS score of 6 or 7) and 4 were of high quality (NOS score of 8 or 9). All studies reported the numbers of corresponding genotypes as to recessive mutants, heterogeneous mutants, and dominant wild types for both case and control groups. Adjusted variables that might affect the ORs were also summarized for each publication (Table 1).

Quantitative data analysis

As shown in Tables 2 and 3, six HOTAIR polymorphisms were analyzed in this meta-analysis. For rs12826786 (C/T), five studies including 1,048 cases and 1,432 controls were evaluated. The fixed-effects models proposed a significant association between C-to-T mutation and cancer risk (TT vs CC+CT: OR =1.55, 95% CI =1.19, 2.03; TT+CT vs CC: OR =1.23, 95% CI =1.04, 1.46; TT vs CC: OR =1.67,

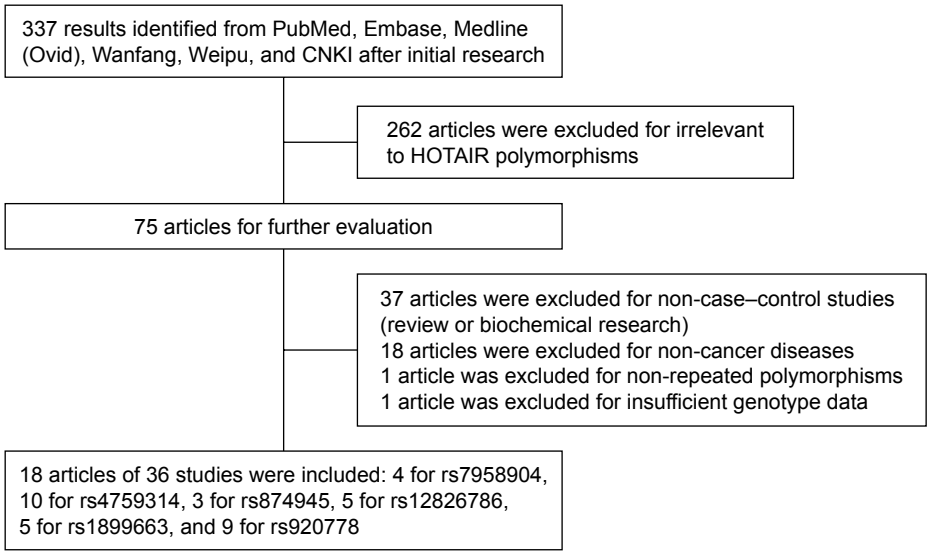

Figure 1 The flow diagram of study selection.
Abbreviation: HOTAIR, HOX transcript antisense intergenic RNA.

Table 1 Characteristics of included studies

Reference	Year	Ethnicity	SNPs	Cancer type	Source of control	Genotyping method	Adjusted factors	Study quality
Bayram et al[25]	2016	Turkish	rs12826786 (C/T)	Breast cancer	Hospital	TaqMan	Age	7
Bayram et al[24]	2015	Turkish	rs920778 (T/C)	Gastric cancer	Hospital	TaqMan	Age, gender, smoking, drinking	7
Bayram et al[25]	2015	Turkish	rs920778 (T/C)	Breast cancer	Hospital	TaqMan	Age, gender	7
Du et al[27]	2015	Chinese	rs4759314 (A/G)	Gastric cancer	Hospital	TaqMan	Age, gender	8
Guo et al[16]	2015	Chinese	rs4759314 (A/G) rs12826786 (C/T)	Gastric cancer	Hospital	PCR-RFLP	Age, gender, smoking status	7
Jin et al[18]	2017	Chinese	rs7958904 (G/C) rs4759314 (A/G) rs874945 (G/A)	Cervical cancer	Hospital	TaqMan	Not known	7
Pan et al[28]	2016	Chinese	rs4759314 (A/G) rs1899663 (G/T) rs920778 (C/T)	Gastric cancer	Population	PCR-RFLP	Age, gender	7
Qiu et al[30]	2016	Chinese	rs920778 (T/C)	Ovarian cancer	Not known	TaqMan	Age, parity, smoking, menopausal status	6
Qiu et al[30]	2016	Chinese	rs920778 (C/T)	Cervical cancer	Not known	TaqMan	Age	6
Taheri et al[31]	2017	Iranian	rs4759314 (A/G) rs12826786 (C/T) rs1899663 (G/T)	Prostate cancer	Hospital	ARMS-PCR	Age, BMI, smoking	7
Ulger et al[17]	2017	Turkish	rs12826786 (C/T)	Gastric cancer	Hospital	TaqMan	Age, gender, smoking, drinking	7
Wu et al[32]	2016	Chinese	rs7958904 (G/C) rs4759314 (A/G) rs874945 (G/A)	Ovarian cancer	Not known	RT-PCR	Age, drinking, BMI	6
Xavier-Magalhães et al[33]	2017	Portuguese	rs12826786 (C/T) rs920778 (C/T)	Glioma	Population	PCR-RFLP	Age, gender	8
Xue et al[19]	2015	Chinese	rs7958904 (G/C) rs4759314 (A/G) rs874945 (G/A)	Colorectal cancer	Hospital	TaqMan	Age, gender, drinking	7
Yan et al[34]	2015	Chinese	rs4759314 (A/G) rs1899663 (G/T) rs920778 (C/T)	Breast cancer	Population	PCR-RFLP	Age, menopause age, menstrual history, No of pregnancy, No of abortion, breast feeding	8
Zhang et al[35]	2014	Chinese	rs4759314 (A/G) rs1899663 (G/T) rs920778 (C/T)	Esophageal cancer	Hospital	RT-PCR	Age, gender	8
Zhu et al[36]	2016	Chinese	rs4759314 (A/G) rs1899663 (G/T) rs920778 (C/T)	Thyroid cancer	Not known	PCR-RFLP	Age, gender	6
Zhu et al[37]	2016	Chinese	rs7958904 (G/C)	Colorectal cancer	Hospital	TaqMan	Age, gender, smoking, drinking, meal regularity, grain intake	7

Abbreviations: ARMS-PCR, amplification-refractory mutation system-polymerase chain reaction; BMI, body mass index; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RT-PCR, real-time polymerase chain reaction; SNP, single-nucleotide polymorphism.

95% CI =1.24, 2.24; T vs C: OR =1.24, 95% CI =1.09, 1.40), while heterozygous mutants alone failed to display statistically significant OR (Figure 2A and B). The results for rs920778 (C/T) were similar. Nine studies with 11,442 participants and seven cancer types were pooled. Recessive mutants presented significantly higher cancer risk when compared with either remaining genotypes or homozygous wild types (TT vs CC+CT: OR =1.73, 95% CI =1.30, 2.30; TT vs CC: OR =1.83, 95% CI =1.25, 2.68). The mutant containing genotypes and mutant allele T also showed statistical significance in elevated cancer risk (TT+CT vs CC: OR =1.40, 95% CI =1.16, 1.70; T vs C: OR =1.37, 95% CI =1.18, 1.59), as shown in Figure 2C and D. The stratified analysis of 10,508 Chinese was consistent with the overall group results. Thus, it can be concluded that rs12826786 (C/T) and rs920778 (C/T) were correlated with increased cancer risk.

The results for rs7958904 (G/C) polymorphisms were less direct. Four studies including 8,816 Chinese participants were analyzed. The meta-analysis showed that the heterozygous mutants alone and combined with recessive mutants posed lower cancer risks (GC vs GG+CC: OR =0.89, 95% CI =0.82–0.98; CC+GC vs GG: OR =0.84, 95% CI =0.71–0.99). Notably, three out of four studies reported that G-to-C mutation could decrease colorectal

Table 2 Genotype distributions of included studies

SNP	References	Year	Cancer type	Case number	Control number	Case			Control		
						Rec	Hetero	Dom	Rec	Hetero	Dom
rs7958904	Jin et al[18]	2017	Cervical caner	1,153	1,292	86	427	640	63	494	735
(G/C)	Wu et al[32]	2016	Ovarian cancer	1,000	1,000	51	355	594	87	380	533
	Xue et al[19]	2015	Colorectal cancer	1,145	1,201	74	399	672	99	456	646
	Zhu et al[36]	2016	Colorectal cancer	394	394	38	141	215	52	161	181
rs4759314	Du et al[27]	2015	Gastric cancer	1,275	1,644	6	186	1,083	8	172	1,464
(A/G)	Guo et al[16]	2015	Gastric cancer	515	654	1	53	461	1	64	589
	Jin et al[18]	2017	Cervical cancer	1,174	1,304	4	158	1,012	2	140	1,162
	Pan et al[28]	2016	Gastric cancer	500	1,000	1	48	451	3	83	914
	Taheri et al[31]	2017	Prostate cancer	125	250	7	32	86	6	81	163
	Wu et al[32]	2016	Ovarian cancer	1,000	1,000	41	140	819	23	125	852
	Xue et al[19]	2015	Colorectal cancer	1,147	1,203	1	135	1,011	9	157	1,037
	Yan et al[34]	2015	Breast cancer	502	504	1	50	451	2	54	448
	Zhang et al[35]	2014	Esophageal cancer	1,000	1,000	2	81	917	1	89	910
	Zhu et al[36]	2016	Thyroid cancer	600	600	2	58	540	2	45	553
rs874945	Jin et al[18]	2017	Cervical cancer	1,171	1,289	43	383	745	43	394	852
(G/A)	Wu et al[32]	2016	Ovarian cancer	1,000	1,000	52	283	665	44	279	677
	Xue et al[19]	2015	Colorectal cancer	1,147	1,202	40	356	751	39	346	817
rs12826786	Bayram et al[25]	2016	Breast cancer	123	122	30	51	42	14	64	44
(C/T)	Guo et al[16]	2015	Gastric cancer	515	654	30	200	285	19	232	403
	Taheri et al[31]	2017	Prostate cancer	128	250	32	70	26	42	125	83
	Ulger et al[17]	2017	Gastric cancer	105	207	20	47	38	35	99	73
	Xavier-Magalhães et al[33]	2017	Glioma	177	199	16	77	84	21	84	94
rs1899663	Pan et al[28]	2016	Gastric cancer	490	1,020	6	118	366	13	255	752
(G/T)	Taheri et al[31]	2017	Prostate cancer	127	250	22	70	35	40	133	77
	Yan et al[34]	2015	Breast cancer	502	361	14	149	339	20	158	326
	Zhang et al[35]	2014	Esophageal cancer	1,000	1,000	19	256	725	26	250	724
	Zhu et al[37]	2016	Thyroid cancer	580	600	7	151	422	12	175	413
rs920778	Bayram et al[24]	2015	Gastric cancer	104	209	32	52	20	66	105	38
(C/T)	Bayram et al[25]	2015	Breast cancer	123	122	40	52	31	41	66	15
	Pan et al[28]	2016	Gastric cancer	800	1,600	59	321	420	45	575	980
	Qiu et al[30]	2016	Ovarian cancer	329	680	25	69	235	22	78	580
	Qiu et al[30]	2016	Cervical cancer	215	430	47	78	90	54	150	226
	Xavier-Magalhães et al[33]	2017	Glioma	177	199	82	71	24	90	84	25
	Yan et al[34]	2015	Breast cancer	502	504	339	151	12	296	190	18
	Zhang et al[35]	2014	Esophageal cancer	2,098	2,150	181	826	1,091	78	749	1,323
	Zhu et al[37]	2016	Thyroid cancer	600	600	53	259	288	19	209	372

Abbreviations: Dom, dominant wild type; Hetero, heterozygous genotype; Rec, recessive genotype; SNP, single-nucleotide polymorphism.

and ovarian cancer risks, while one study pointed that CC genotype was related to increased cervical cancer risk. Therefore, it is hard to conclude that rs7958904 (G/C) polymorphisms are related to overall cancer susceptibility. However, this inconsistency indicated that rs7958904 (G/C) polymorphisms might play different roles in different types of cancer.

As to the remaining three types of polymorphisms (rs4759314, rs874945, and rs1899663), no significant association was found between mutant genotypes (or alleles) and cancer susceptibility in the corresponding effect models, either for overall population or for Chinese subgroups. Even though allele A implied a cancer-prone tendency (A vs G: OR =1.09; 95% CI =1.00–1.18) in rs874945 (G/A) polymorphisms, it is impossible to draw any significant conclusion.

Publication bias

The publication bias was first assessed by visually examining the funnel plots (Figure 3). Studies on rs4759314, rs874945, rs12826786, and rs1899663 were symmetric, while the existence of bias was indicated in rs7958904 and rs920778. Egger's test was then performed in the two polymorphisms. The results demonstrated no significant bias in the two polymorphisms ($P>0.05$, data not shown).

Table 3 Summary of different comparative results of HOTAIR polymorphisms on cancer susceptibility

SNP	Comparative type	Overall and subgroup	Participants	OR (95% CI)	*Z*-value	*P*-value	I^2 (%)	Effect model
rs7958904 (G/C)	CC vs GG+GC	Overall	8,816	0.82 (0.53, 1.27)	0.78	0.38	85	R
	CC+GC vs GG	Overall	8,816	0.84 (0.71, 0.99)	2.06	0.04	71	R
	GC vs GG+CC	Overall	7,579	0.89 (0.82, 0.98)	2.52	0.01	0	F
	CC vs GG	Overall	4,766	0.77 (0.47, 1.24)	1.08	0.28	87	R
	C vs G	Overall	15,158	0.86 (0.72, 1.03)	1.67	0.10	85	R
rs4759314 (A/G)	GG vs AA+AG	Overall	18,235	1.37 (0.96, 1.94)	1.74	0.08	0	F
		Chinese	17,860	1.29 (0.89, 1.87)	1.34	0.18	0	F
	GG+AG vs AA	Overall	18,235	1.11 (0.97, 1.27)	1.50	0.13	52	R
		Chinese	17,860	1.13 (0.98, 1.30)	1.70	0.09	54	R
	AG vs AA+GG	Overall	18,235	1.09 (0.95, 1.25)	1.22	0.22	51	R
		Chinese	17,860	1.12 (1.02, 1.23)	2.38	0.02	47	F
	GG vs AA	Overall	16,140	1.38 (0.97, 1.96)	1.78	0.08	0	F
		Chinese	15,878	1.31 (0.90, 1.90)	1.42	0.15	0	F
	G vs A	Overall	36,470	1.12 (0.98, 1.27)	1.64	0.10	54	R
		Chinese	35,720	1.13 (0.98, 1.30)	1.66	0.10	58	R
rs874945 (G/A)	AA vs GG+GA	Overall	6,809	1.13 (0.88, 1.44)	0.95	0.34	0	F
	AA+GA vs GG	Overall	6,809	1.10 (0.99, 1.21)	1.84	0.07	0	F
	GA vs GG+AA	Overall	6,809	1.08 (0.98, 1.20)	1.50	0.13	0	F
	AA vs GG	Overall	4,768	1.16 (0.90, 1.48)	1.14	0.26	0	F
	A vs G	Overall	13,618	1.09 (1.00, 1.18)	1.90	0.06	0	F
rs12826786 (C/T)	TT vs CC+CT	Overall	2,480	1.55 (1.19, 2.03)	3.21	0.01	40	F
	TT+CT vs CC	Overall	2,480	1.23 (1.04, 1.46)	2.47	0.01	29	F
	CT vs CC+TT	Overall	2,480	1.04 (0.89, 1.23)	0.50	0.62	23	F
	TT vs CC	Overall	1,431	1.67 (1.24, 2.24)	3.41	0.01	48	F
	T vs C	Overall	4,960	1.24 (1.09, 1.40)	3.35	0.01	35	F
rs1899663 (G/T)	TT vs GG+GT	Overall	6,073	0.82 (0.60, 1.12)	1.24	0.22	0	F
		Chinese	5,696	0.72 (0.50, 1.05)	1.68	0.09	0	F
	TT+GT vs GG	Overall	6,073	0.94 (0.84, 1.05)	1.14	0.25	0	F
		Chinese	5,696	0.92 (0.82, 1.04)	1.34	0.18	0	F
	GT vs GG+TT	Overall	6,073	0.96 (0.86, 1.08)	0.70	0.49	0	F
		Chinese	5,696	0.97 (0.85, 1.10)	0.50	0.62	0	F
	TT vs GG	Overall	4,358	0.81 (0.59, 1.12)	1.26	0.21	0	F
		Chinese	4,184	0.71 (0.49, 1.04)	1.76	0.08	0	F
	T vs G	Overall	12,146	0.93 (0.85, 1.03)	1.38	0.17	0	F
		Chinese	11,392	0.92 (0.83, 1.02)	1.66	0.10	0	F
rs920778 (C/T)	TT vs CC+CT	Overall	11,442	1.73 (1.30, 2.30)	3.79	0.01	77	R
		Chinese	10,508	2.21 (1.72, 2.85)	6.15	0.01	61	R
	TT+CT vs CC	Overall	11,442	1.40 (1.16, 1.70)	3.45	0.01	72	R
		Chinese	10,508	1.55 (1.43, 1.69)	10.22	0.01	43	F
	CT vs CC+TT	Overall	11,442	1.10 (0.91, 1.32)	0.99	0.32	77	R
		Chinese	10,508	1.20 (0.97, 1.48)	1.71	0.09	81	R
	TT vs CC	Overall	7,357	1.83 (1.25, 2.68)	3.10	0.01	79	R
		Chinese	6,853	2.76 (2.31, 3.29)	11.22	0.01	0	F
	T vs C	Overall	22,884	1.37 (1.18, 1.59)	4.10	0.01	79	R
		Chinese	21,016	1.56 (1.41, 1.74)	8.26	0.01	53	R

Abbreviations: F, fixed-effects model; OR, odds ratio; HOTAIR, HOX transcript antisense intergenic RNA; R, random-effects model; SNP, single-nucleotide polymorphism.

Discussion

lncRNAs are a crucial class of RNAs involved in multiple biologic processes such as proliferation and progression of cancer, despite so often being branded as transcriptional noise.[38,39] Especially, lncRNA HOTAIR, which is coded from the HOXC locus, has been identified to participate in the development and metastasis of malignancies.[40,41] Several biochemical studies suggested that HOTAIR could not only increase Polycomb Repressive Complex 2 recruitment to the genomic positions of target genes to promote malignant transformation but also sponge miR-331-3p to regulate HER2 expression.[42–44] Clinically, unregulated expression

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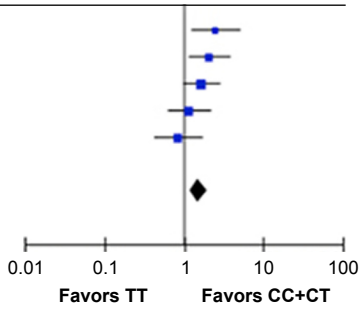
Study or subgroup	Case Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Bayram et al[25]	30	123	14	122	12.5	2.49 (1.25, 4.97)
Guo et al[16]	30	515	19	654	18.6	2.07 (1.15, 3.72)
Taheri et al[31]	32	128	42	250	25.2	1.65 (0.98, 2.78)
Xavier-Magalhães et al[33]	20	105	35	207	22.5	1.16 (0.63, 2.12)
Ulger et al[17]	16	177	21	199	21.2	0.84 (0.42, 1.67)
Total (95% CI)		**1,048**		**1,432**	**100**	**1.55 (1.19, 2.03)**
Total events	128		131			

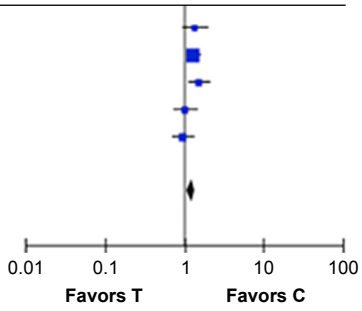
Heterogeneity: χ^2=6.72, *df*=4 (*P*=0.15); I^2=40%
Test for overall effect: *Z*=3.21 (*P*=0.001)



B

Study or subgroup	Case Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Bayram et al[25]	111	246	92	244	11.4	1.36 (0.95, 1.95)
Guo et al[16]	260	1,030	270	1,308	40.0	1.30 (1.07, 1.58)
Taheri et al[31]	134	256	209	500	15.2	1.53 (1.13, 2.07)
Xavier-Magalhães et al[33]	87	210	169	414	15.0	1.03 (0.73, 1.44)
Ulger et al[17]	109	354	126	398	18.5	0.96 (0.71, 1.31)
Total (95% CI)		**2,096**		**2,864**	**100**	**1.24 (1.09, 1.40)**
Total events	701		866			

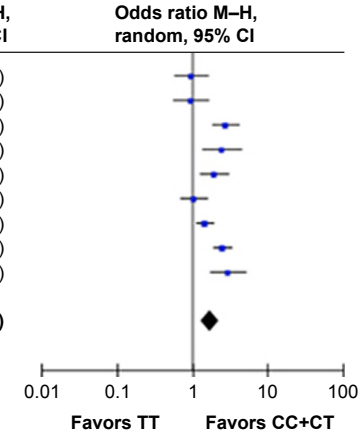
Heterogeneity: χ^2=6.14, *df*=4 (*P*=0.19); I^2=35%
Test for overall effect: *Z*=3.35 (*P*=0.0008)



C

Study or subgroup	Case Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Bayram et al[24]	32	104	66	209	10.2	0.96 (0.58, 1.60)
Bayram et al[26]	40	123	41	122	9.9	0.95 (0.56, 1.62)
Pan et al[28]	59	800	45	1,600	11.6	2.75 (1.85, 4.09)
Qiu et al[30]	25	329	22	680	9.2	2.46 (1.37, 4.43)
Qiu et al[30].*	47	215	54	430	11.2	1.95 (1.27, 3.00)
Xavier-Magalhães et al[33]	82	177	90	199	11.5	1.05 (0.70, 1.57)
Yan et al[34]	339	502	296	504	13.4	1.46 (1.13, 1.89)
Zhang et al[35]	181	2,098	78	2,150	13.2	2.51 (1.91, 3.29)
Zhu et al[36]	53	600	19	600	9.8	2.96 (1.73, 5.07)
Total (95% CI)		**4,948**		**6,494**	**100**	**1.73 (1.30, 2.30)**
Total events	858		711			

Heterogeneity: τ^2=0.14; χ^2=35.23, *df*=8 (*P*<0.0001); I^2=77%
Test for overall effect: *Z*=3.79 (*P*=0.0001)



D

Study or subgroup	Case Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Bayram et al[24]	116	208	237	418	8.7	0.96 (0.69, 1.35)
Bayram et al[26]	132	246	148	244	8.2	0.75 (0.52, 1.08)
Pan et al[28]	439	1,600	665	3,200	13.7	1.44 (1.25, 1.66)
Qiu et al[30]	119	658	122	1,360	10.3	2.24 (1.71, 2.94)
Qiu et al[30].*	172	430	258	860	11.0	1.56 (1.22, 1.98)
Xavier-Magalhães et al[33]	235	354	264	398	9.5	1.00 (0.74, 1.36)
Yan et al[34]	829	1,004	782	1,008	11.6	1.37 (1.10, 1.71)
Zhang et al[35]	1,188	4,196	905	4,300	14.5	1.48 (1.34, 1.64)
Zhu et al[36]	365	1,200	247	1,200	12.5	1.69 (1.40, 2.03)
Total (95% CI)		**9,896**		**12,988**	**100**	**1.37 (1.18, 1.59)**
Total events	3,595		3,628			

Heterogeneity: τ^2=0.04; χ^2=37.47, *df*=8 (*P*<0.00001); I^2=79%
Test for overall effect: *Z*=4.10 (*P*<0.0001)

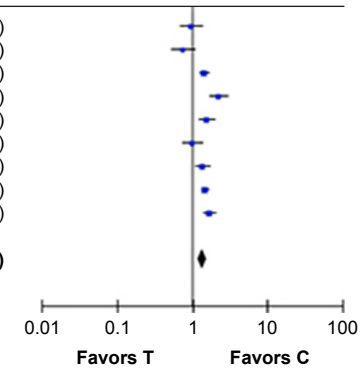


Figure 2 Representative forest plots.
Notes: (**A**) TT vs CC+TT of rs12826786 (C/T) polymorphisms. (**B**) T vs C of rs12826786 (C/T) polymorphisms. (**C**) TT vs CC+TT in overall group analysis of rs920778 (C/T) polymorphisms. (**D**) T vs C in overall group analysis of rs920778 (C/T) polymorphisms. *Cervical cancer group.
Abbreviation: *df*, degrees of freedom.

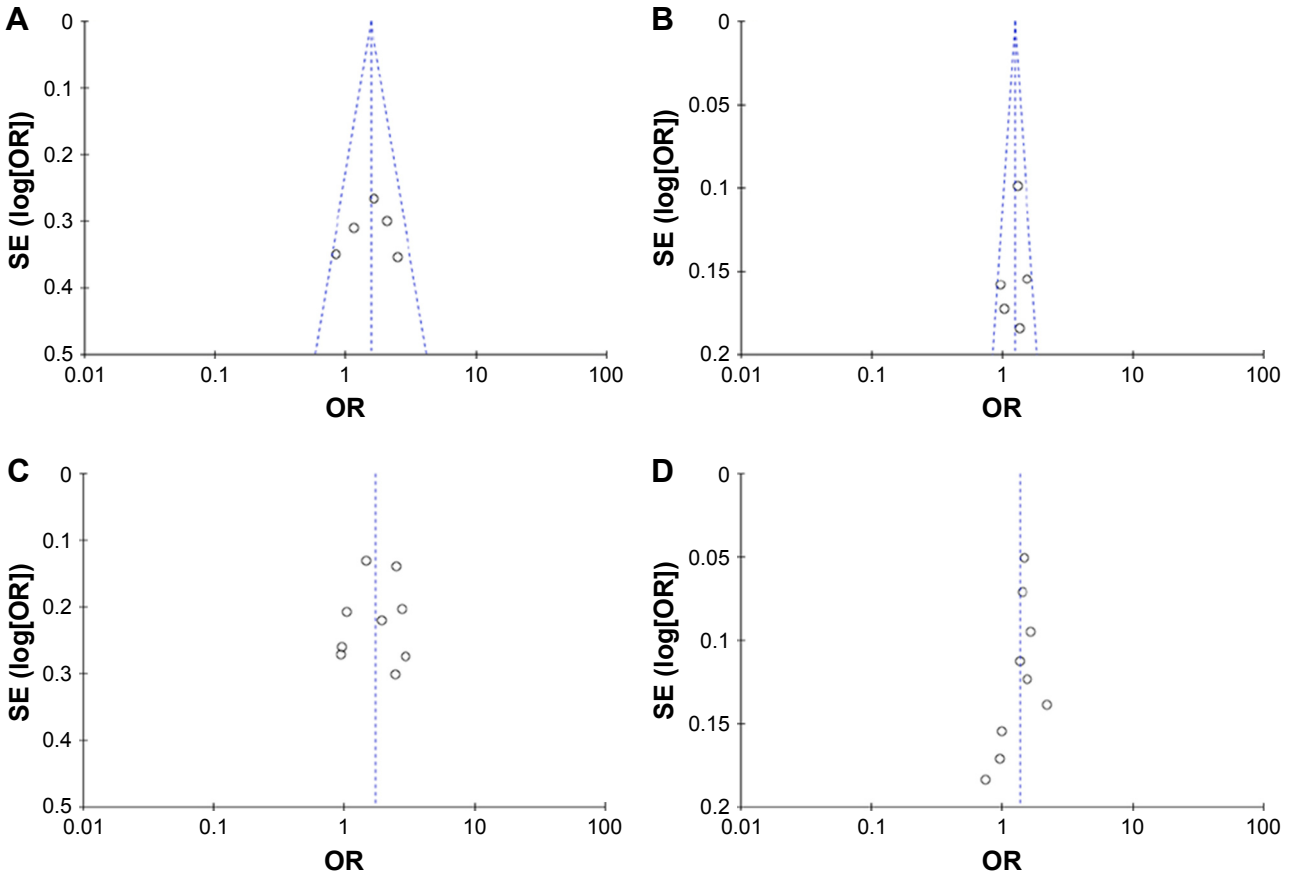


Figure 3 Representative funnel plots of publication bias.
Notes: (**A**) TT vs CC+TT of rs12826786 (C/T) polymorphisms. (**B**) T vs C of rs12826786 (C/T) polymorphisms. (**C**) TT vs CC+TT in overall group analysis of rs920778 (C/T) polymorphisms. (**D**) T vs C in overall group analysis of rs920778 (C/T) polymorphisms.
Abbreviations: OR, odds ratio; SE, standard error.

of HOTAIR was found to be a powerful indicator of poor prognosis for several cancers.[45,46] Since the *Homo sapiens* HOTAIR gene contains many SNPs, recent molecular epidemiologic studies have focused on the association between HOTAIR polymorphisms and cancer susceptibility. Although multiple SNPs and cancer types were explored, no consensus was reached, possibly due to limited sample sizes and variant participant characteristics. In order to draw a more concrete conclusion, we comprehensively searched the existing publications and performed a meta-analysis for six HOTAIR polymorphisms and 10 cancer types by enrolling 36 studies from 18 articles.

Our results showed that polymorphisms of rs12826786 (C/T) and rs920778 (C/T) were correlated with increased cancer risk. Both T-containing genotypes and T alleles were correlated with cancer susceptibility, especially in Chinese population. HOTAIR rs12826786 (C/T) and rs920778 polymorphisms are respectively located within an intronic promoter region and enhancer region, where specific mutations may exert a genotype-specific transcriptional effect on HOTAIR expression.[33,35] Previous luciferase assay showed that the substitution of cytosine (C) by thymine (T) in either of the two loci could result in a higher HOTAIR expression, which was pervasively detected in both primary and metastasized tumors of breast cancer, colorectal cancer, lung cancer, and others.[19,23,24] Moreover, recent case–control studies revealed that high expression of HOTAIR was correlated with lower survival rates.[29,33,37]All these findings are consistent with the results of this meta-analysis, highlighting the roles of SNPs in cancer risk and prognosis.

Our meta-analysis also indicated that the remaining four polymorphisms (rs7958904, rs4759314, rs874945, and rs1899663) were not associated with cancer risk. We noticed that the results for rs7958904 (G/C) polymorphisms were different from a previous meta-analysis, which indicated a decreased cancer risk for G-to-C mutation. The reason lies in the inclusion of the cervical cancer study.[18] The authors discovered that the rs7958904 (G/C) polymorphisms conferred an increased risk of cervical cancer. By performing functional assay and MTT assay, they found a higher HOTAIR

expression in cervical cancer tissues with rs7958904 CC genotype and a growth-promoting role of rs7958904 C allele on cervical cancer cell line. However, the other three studies reported opposite results in both case–control studies and biochemical assays.[19,32,37]As a result, our meta-analysis showed an insignificant result. This reflects the complex function of HOTAIR gene and its variants.[18] It also suggests that HOTAIR polymorphisms might play different biologic roles in different types of cancer.

Despite our efforts to include all the eligible publications, several limitations to our meta-analysis should be noticed. First, the populations of included studies were Chinese, Turkish, Iranian, and Portuguese. It is epidemiologically known that other ethnicities such as blacks and Hispanics are also caner susceptible;[47,48] thus, the lack of data for these populations might affect the overall results. However, it is worth noting that our stratified analysis may draw a more convincing conclusion for Chinese population. Second, our evaluation mainly focused on unadjusted results due to the insufficient data of several risk factors, while the majority of studies only matched age and gender between cases and controls; the possible imbalance among risk factors may cause distorted results. Moreover, although the number of pooled participants was so far the largest, the included cancer types were still limited. Thus, caution must be preserved when explaining the results to other cancers, especially when we noticed that HOTAIR polymorphisms might function differently in different cancers. Therefore, more studies on various cancer types are needed to help reach a consensus.

In conclusion, our meta-analysis showed that HOTAIR polymorphisms of rs12826786 and rs920778 were correlated with increased cancer risk, while rs7958904, rs4759314, rs874945, and rs1899663 were not. Our meta-analysis was the first to explore the relationship between rs12826786 polymorphisms and cancer susceptibility. It also raised the statistic evidence of discrepant HOTAIR behaviors in different cancer types. Clarifying the environmental and lifestyle risk factors and exploring wider types of cancer are required for future studies to help us draw a concrete conclusion.

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Disclosure

The authors report no conflicts of interest in this work.

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