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ORIGINAL ARTICLE

Association between *HOTAIR* polymorphisms and cancer risk: a meta-analysis based on twenty-one case-control studies

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Summary

Purpose: *Previous studies have identified the association between single nucleotide polymorphisms (SNPs) of long non-coding RNA (lncRNA) HOX transcript antisense RNA (HOTAIR) and various cancers risk. Herein, we conducted a meta-analysis to investigate the effects of HOTAIR polymorphisms on multiple cancers risk.*

Methods: *Relevant studies published from July 2014 to October 2017 were identified in the PubMed, EmBase and Web of Science databases. A total of 21 studies including 13,675 cases and 16,306 controls were selected, and the genotypes were mainly confirmed by TaqMan allelic discrimination and PCR-RFLP. Meta-analysis was conducted by STATA 12.0 software and odds ratios (ORs) with their 95% confidence interval (95% CI) were used to estimate the associations between HOTAIR polymorphisms and multiple cancers risk.*

Results: *Twenty-one case-control studies with 13,675 cases and 16,306 controls met our inclusion criteria. Our results showed a significant association between HOTAIR rs920778 polymorphism and increased cancer risk under all five genetic models, as well as in Asians subgroup analysis based on ethnicity, digestive and gynecologic cancer group based on cancer type. For rs12826786 C>T polymorphism, we found a similarly increased risk in Asians group under the allele, dominant, homozygote and recessive models.*

Conclusions: *Our findings indicate that the T allele or TT genotype of HOTAIR polymorphisms may serve as a potential genetic marker for cancer risk, especially in Asians. However, there is no significant association between SNPs variants and cancer risk under any five genetic models for rs4759314, rs1899663 and rs874945.*

Key words: *cancer risk, HOTAIR, lncRNA, HOX transcript antisense intergenic RNA, meta-analysis, polymorphism*

Introduction

The genome sequencing projects have shown that less than 2% of the mammalian genome is in protein-encoded regions, and more than 90% of the genome is transcribed as noncoding RNAs (ncRNAs) [1,2].These ncRNAs are classified as short and long ncRNAs based on the length of nucleotides (nt). Long non-coding RNAs (lncRNAs) are longer than 200 nt (frequently up to 100 kbp) [3]. And it has been reported that lncRNAs play a crucial role in a wide range of biological processes, including chromatin remodeling, genome packaging, genome rearrangement, dosage compensation, gene imprinting, and regulation of gene expression [4-7]. Thus, lncRNAs have been arousing highly interests

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among cancer researchers due to their ability to local or global regulation of gene expression via epigenetic, transcriptional or post-transcriptional mechanisms [8]. The application of genome-wide association studies (GWAS) and next-generation sequencing (NGS) in exploring cancer-related genes have greatly broadened our understanding of the genetic variations. Recently, a number of studies have reported that lncRNAs were deregulated in various cancers, and their polymorphisms were significantly associated with cancers [9-12]. *HOX* transcript antisense intergenic RNA (*HOTAIR*), one of these cancer-related molecules, has been demonstrated as an oncogenic factor in the development of different cancers [13-17].

HOTAIR is a 2158-nuleotide lncRNA transcribed from the antisense strand of the *homeobox C* (*HOXC*) genes cluster that are located in chromosome *12q13.12* [18]. Recent studies have reported that the major role of *HOTAIR* involves epigenetic regulation of transcription in 40 kb region of *HOXD* by modifying chromatin structure [13,18,19]. It has been revealed that *HOTAIR* could interact with *PRC2* and induce its relating methylation of *H3K27* to reprogram chromatin organization [18,19]. Moreover, overexpression of *HOTAIR* could accelerate tumor growth through suppressing apoptosis, promoting cell cycle progression, and increase cellular migration and invasion in different types of cancers [20-22]. All those convincing proofs indicate the oncogenic role of *HOTAIR* in various cancers.

Recently, considerable efforts have been made to investigate the association between the lncRNA variations and the susceptibility of cancers. In particular, the *HOTAIR* variations have been demonstrated to be closely related to the development and progression of some cancers [23-25]. Recent studies suggested that SNPs of *HOTAIR* (such as rs920778, rs4759314, rs1899663, rs12826786, rs874945, rs7958904 and rs10783618) acted as potential cancer susceptibility loci and were significantly associated to the increase of the risk of various cancers, including esophageal squamous cell carcinoma [26], gastric cancer [27-29], colorectal cancer [30], gastric cardia adenocarcinoma [31], breast cancer [16,32-35], cervical cancer [36-38], papillary thyroid carcinoma [39], ovarian cancer [40], glioma [41], and prostate cancer [27,42]. However, although an increasing number of investigations are drawing attention to the relationship be-

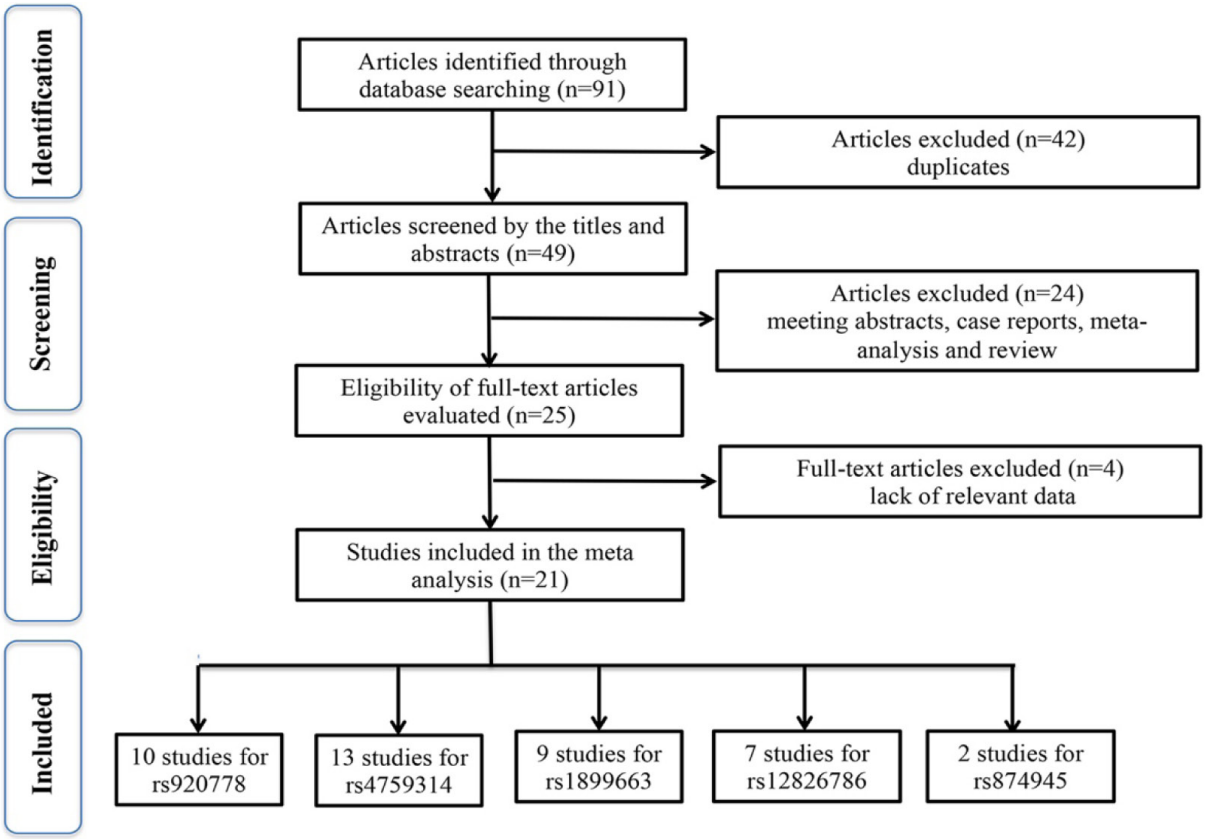

Figure 1. The flow diagram of this meta-analysis. A total of 21 studies were selected in this meta-analysis. Ten studies on rs920778 C>T, 13 on rs4759314 A>G, 9 studies on rs1899663 G>T, 7 studies on rs12826786 C>T and 2 studies on rs874945 G>A were eligible according to the exclusion criteria.

tween *HOTAIR* polymorphisms and cancer risk, the obtained results so far have still been controversial and inconclusive [43-48]. Moreover, most individual studies have been limited by small sample sizes. Thus, we performed an up-to-date meta-analysis to assess a more precise estimate of the possible associations.

Methods

Search strategy

The PubMed, EmBase and Web of Science databases were searched for identifying studies that examined the association between *HOTAIR* polymorphisms and cancer risk up to October 20, 2017. The comprehensive literature search was using following key words: "cancer or neoplasms or carcinoma or tumor", "Hox transcript antisense intergenic RNA or *HOTAIR*", "long non-coding RNA or lncRNA", "Polymorphism Single Nucleotide or SNP or polymorphism" to summarize the studies of association between *HOTAIR* polymorphisms and cancer risk.

Literature retrieval strategy

Eligible studies for this meta-analysis were only those written in English with full-text. All selected studies should meet the following criteria: (1) published studies based on case-control or cohort study design evaluating the association between *HOTAIR* polymorphisms and cancer risk; (2) adequate data available about

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

First author	*Year*	*Region*	*Ethnicity*	*Tumor Type*	*Case/ Control*	*Source of control*	*Platform*	*Genotyped SNPs*			*NOS*
Xavier	2017	Portugal	Caucasian	GM	177/199	HB	PCR-RFLP	rs920778	rs12826786		8
Wang	2017	China	Asian	NIHL	570/570		Sequenom MassARRAY	rs874945	rs7958904		8
Ulger	2017	Turkey	Caucasian	GC	105/207	HB	TaqMan	rs12826786			7
Taheri	2017	Iran	Caucasian	PC	128/250	HB	ARMS-PCR	rs1899663	rs12826786	rs4759314	7
Taheri	2017	Iran	Caucasian	BPH	128/250	HB	ARMS-PCR	rs1899663	rs12826786	rs4759314	7
Qiu	2017	China	Asian	OC	329/680	HB	TaqMan	rs920778			7
Khorshidi	2017	Iran	Caucasian	BC	122/200	HB	ARMS-PCR	rs4759314	rs12826786	rs1899663	8
Jin	2017	China	Asian	CC	1209/1348	HB	TaqMan	rs7958904	rs4759314	rs874945	7
Hu	2017	China	Asian	PCC	416/416	HB	TaqMan	rs4759314			7
Hassanzarei	2017	Iran	Caucasian	BC	220/231	PB	PCR-RFLP	rs920778 rs1899663	rs12826786	rs4759314	7
Zhu	2016	China	Asian	PTC	2400/2400	HB	PCR-RFLP	rs920778	rs4759314	rs1899663	7
Qiu	2016	China	Asian	CC	215/430	HB	TaqMan	rs920778			7
Pan	2016	China	Asian	GC	800/1600	HB	PCR-RFLP	rs920778	rs4759314	rs1899663	7
Guo	2016	China	Asian	CC	510/713	HB	MALDI-TOF mass	rs920778	rs12826786	rs4759314	7
Bayram	2015	Turkey	Caucasian	BC	123/122	HB	TaqMan	rs12826786			8
Yan	2015	China	Asian	BC	502/504	PB	CRS-RFLP/ PCR-RFLP	rs920778	rs4759314	rs1899663	8
Xue	2015	China	Asian	CRC	1734/1855	HB	TaqMan	rs4759314			7
Guo	2015	China	Asian	GCA	515/654	HB	PCR-RFLP	rs12826786	rs4759314	rs10783618	7
Bayram	2015	Turkey	Caucasian	GC	104/209	HB	TaqMan	rs920778			7
Bayram	2015	Turkey	Caucasian	BC	123/122	HB	TaqMan	rs920778			7
Du	2015	China	Asian	GC	1275/1646	HB	TaqMan	rs4759314			8
Zhang	2014	China	Asian	ESCC	2098/2150	HB	PCR-RFLP	rs920778	rs4759314	rs1899663	8

GM: glioma, NIHL: noise-induced hearing loss, GC: gastric cancer, PC: prostate cancer, BPH: benign prostate hyperplasia, OC: ovarian cancer, BC: breast cancer, CC: cervical cancer, PCC: pancreatic cancer, PTC: papillary thyroid carcinoma, CRC: colorectal cancer, GCA: gastric cardia adenocarcinoma, ESCC: esophageal squamous cell carcinoma, HB: hospital-based, PB: population-based, PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism, CRS-RFLP: created-restriction-site PCR-RFLP. The study design of all selected articles is case-control.

the genotype frequency of *HOTAIR* SNPs rs920778, rs4759314, rs1899663, rs12826786 or rs874945; (3) the odds ratios (ORs) were available or could be calculated with 95% confidence intervals (CIs). The exclusion criteria were the following: (1) studies investigating the progression, severity, phenotype modification, response to treatment, survival and family; (2) meeting abstracts, case reports, editorials and reviews. Ultimately, a total of 21 articles including 13,675 cases and 16,306 controls were dovetailed into this meta-analysis.

Data extraction

Two investigators (Tian Xu and Yu Zhou) independently extracted the following data from each included study: surname of first author, year of publication, region of patients, ethnicity of patients, type of cancers, numbers of cases and controls, p value for Hardy-Weinberg equilibrium (HWE) in control, study design, source of control, platform of genotyping and genotype of SNPs. Different ethnicity descents were categorized as Asians or Caucasians. The results were compared and disagreement was resolved by discussion with a third reviewer (Shikai Zhu) until consensus was reached.

Quality assessment

The quality of the included studies was assessed based on the Newcastle-Ottawa quality assessment scale (NOS). NOS was used to evaluate the methodological quality, which scored studies based on three factors: selection, comparability and exposure[49]. A study awarded a score of 0 - 3, 4 - 6, or 7 - 9 was considered as a low-, moderate-, or high-quality study, respectively.

Statistics

The ORs with 95% CIs were used to assess the strength of the association between the *HOTAIR* polymorphisms and cancer risk. Five different comparison models, including allele, dominant, homozygote, heterozygote and recessive model, were used to obtain a more comprehensive assessment of associations between *HOTAIR* polymorphisms and cancer risk. For the *HOTAIR* rs920778 C>T polymorphisms, the pooled ORs were assessed for allele model (T vs C), dominant model (TC+TT vs CC), heterozygote model (TC vs CC), homozygote model (TT vs CC) and recessive model (TT vs TC+CC). Similar genetic models were also obtained for *HOTAIR* rs4759314 A>G, rs1899663 G>T, rs12826786 C>T and rs874945 G>A variants. And subgroup analyses were applied based on ethnicity and cancer type. The fixed-effects model was adopted to calculate ORs if heterogeneity was high ($P_{heterogeneity}$> 0.05 and/or I2 < 50%) [50]. Otherwise, a random-effects model was used [51]. Sensitivity analysis was conducted by sequentially excluding each study. The publication bias of this study was performed by Begg's and Egger's tests. The trim-and-fill method was used to identify and adjust for those studies if any possible bias was observed. Data analyses were carried out by using Stata software, version 12.0 (Stata Corporation; College Station, TX, USA). P values < 0.05 were considered statistically significant.

Results

Study selection and characteristics

A total of 91 relevant articles were identified based on electronic databases including PubMed, EmBase and Web of Science. The study selection process is shown in Figure 1. In this meta-analysis, 70 studies were excluded due to different deficiencies. Ultimately, 21 eligible articles were selected with adequate data, including 10 studies on rs920778 C>T, 13 studies on rs4759314 A>G, 9 studies on rs1899663 G>T, 7 studies on rs12826786 C>T and 2 studies on rs874945, respectively. The articles were published between July 2014 to October 2017. The studies were performed in Turkey (n=4), China (n=13), Portugal (n=1) and Iran (n=3). Thirteen types of human cancers, including esophageal squamous cell carcinoma (n=1), gastric cancer (n=4), colorectal cancer (n=1), gastric cardia adenocarcinoma (n=1), breast cancer (n=3), cervical cancer (n=3), papillary thyroid carcinoma (n=1), ovarian cancer (n=1), glioma (n=1), prostate cancer (n=1) and benign prostate hyperplasia (n=1) were recorded in this meta-analysis. The design of all included studies were case-control and the source of control were from hospital-based (n=19) or population-based (n=2) persons. A more detailed characteristics of the selected studies are shown in Table 1.

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

A total of 10 studies containing 7,258 cases and 9,007 controls were examined for the association between the *HOTAIR* rs920778 C>T polymorphism and cancer risk (Supplementary Table 1). The combined analyses exhibited a significantly increased risk of cancer for *HOTAIR* rs920778 in all 5 genetic models [T versus C (allele model): OR=1.44; 95% CI=1.31-1.57, CT+TT versus CC (dominant model): OR=1.45; 95% CI=1.36-1.55 CT versus CC (heterozygote model): OR=1.32; 95% CI=1.23-1.42, TT versus CC (homozygote model): OR=2.35; 95% CI=2.05-2.69, TT versus CC+CT (recessive model): OR=1.97; 95% CI=1.62-2.39] (Supplementary Table 2). Furthermore, we evaluated the effect of the rs920778 on cancer risk among the subgroups based on ethnicity and cancer type. In a stratified analysis of rs920778 polymorphism based on cancer type, a significantly increased cancer risk was observed among digestive cancer (allele model: OR=1.40; 95% CI=1.23-1.60; dominant model: OR=1.44; 95% CI=1.31-1.59; heterozygote model: OR=1.31; 95% CI=1.19-1.45; homozygote model: OR=2.32; 95% CI =1.45-3.69; recessive model: OR=2.08; 95%

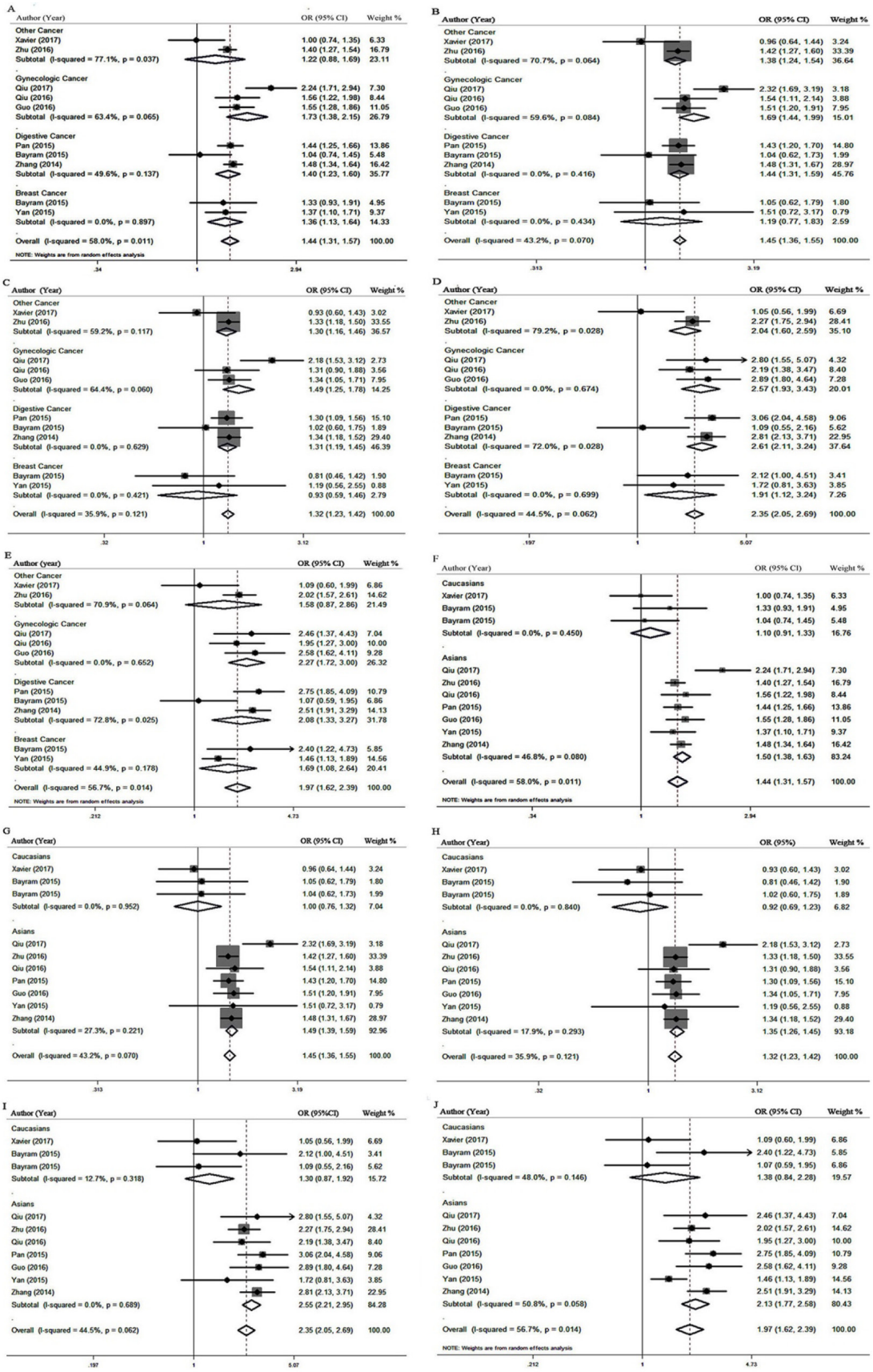

Figure 2. Forest plot of cancer risk in different cancer types and ethnicities associated with HOTAIR polymorphism rs920778 under different models. Models represented: **A:** allele model based on cancer types; **B:** dominant model based on cancer types; **C:** heterozygote model based on cancer types; **D:** homozygote model based on cancer types; **E:** recessive model based on cancer types; **F:** allele model based on ethnicities; **G:** dominant model based on ethnicities; **H:** heterozygote model based on ethnicities; **I:** homozygote model based on ethnicities; **J:** recessive model based on ethnicities.

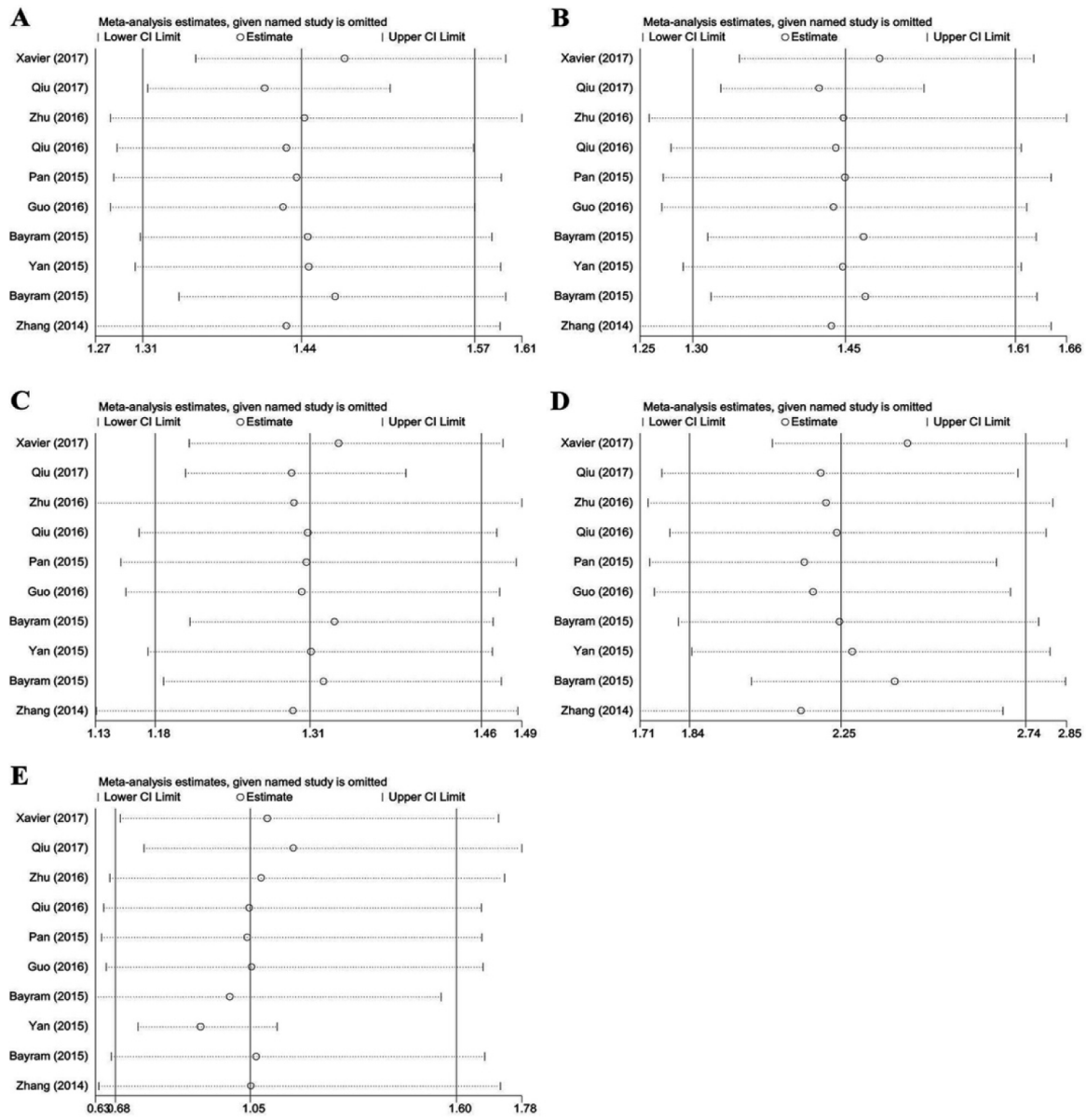

Figure 3. Sensitivity analysis for rs920778 in this meta-analysis. There figures show the influence of individual studies on the summary OR in different models. The middle vertical axis indicates the overall OR and the two vertical axes indicate the 95% CI. Open circles indicate the pooled OR when the 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. Models represented: **A:** allele model; **B:** dominant model; **C:** heterozygote model; **D:** homozygote model; **E:** recessive model.

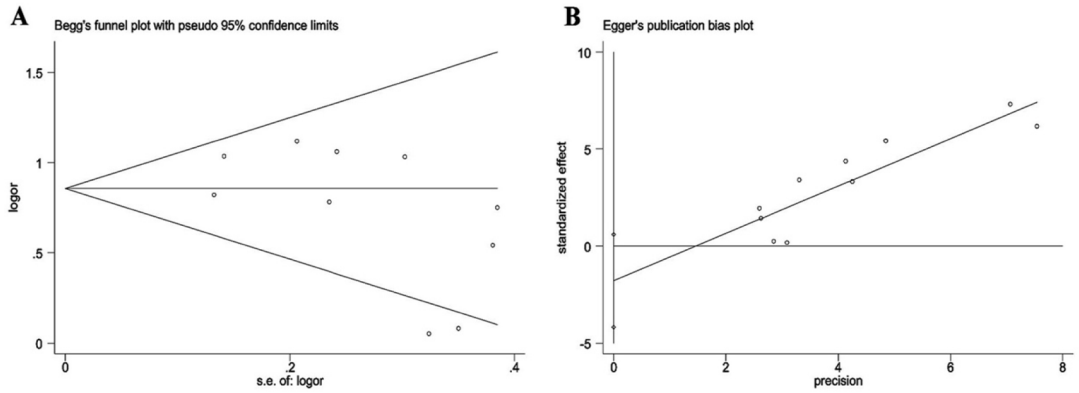

Figure 4. Begg's funnel plot and Egger's plot for publication bias for rs920778. Each point represents a separate study for the indicated association. **A:** Begg's funnel plot; **B:** Egger's publication bias plot.

CI=1.33-3.27) and gynecologic cancer (allele model: OR=1.73; 95% CI=1.38-2.15; dominant model: OR=1.69; 95% CI=1.44-1.99; heterozygote model: OR=1.49; 95% CI=1.25-1.78; homozygote model: OR=2.57; 95% CI =1.93-3.43; recessive model: OR=2.08; 95% CI=1.33-3.27 (Figure 2A-E). A significantly increased cancer risk was observed among Asians (allele model: OR=1.50; 95% CI=1.37-1.65; dominant model: OR=1.52; 95% CI=1.36-1.68; heterozygote model: OR=1.37; 95% CI=1.24-1.52; homozygote model: OR=2.52; 95% CI=2.16-2.94; recessive model: OR=2.09; 95% CI=1.70-2.57). In contrast, there was no significant association between rs920778 and cancer risk among Caucasians (allele model: OR=1.10; 95% CI=0.91-1.33; dominant model: OR=1.00; 95% CI=0.77-1.30; heterozygote model: OR=0.92; 95% CI=0.69-1.23; homozygote model: OR=1.30; 95% CI=0.85-1.98; recessive model: OR=1.39; 95% CI=0.84-2.94) (Figure 2F-J). Sensitivity analysis showed that no single study qualitatively changed the pooled ORs with corresponding 95% CI, indicating that those data were highly stable. Visual inspection of funnel plot did not reveal any asymmetrical evidence (Figure 3). The data were further supported by the Begg's and Egger's tests. No publication bias was observed, indicating that the results were statistically robust (Figure 4).

Association between the HOTAIR rs12826786 C>T polymorphism and cancer risk

A total of 8 studies including 1,532 cases and 2,113 controls were examined for the association between the *HOTAIR* rs12826786 C>T polymorphism and cancer risk (Supplementary Table 1). The combined analyses exhibited a significantly increased risk of cancer for *HOTAIR* rs12826786 in 4 of 5 genetic models [T versus C (allele model): OR=1.22; 95% CI=1.05-1.41, CT+TT versus CC (dominant model): OR=1.22; 95% CI=1.04-1.44, CT versus CC (heterozygote model): OR=1.15; 95% CI=0.99-1.35, TT versus CC (homozygote model): OR=1.57; 95% CI=1.10-2.24, TT versus CC+CT (recessive model): OR=1.454; 95% CI=1.06-1.99] (Supplementary Table 2). We next evaluated the effect of the rs12826786 on cancer risk among the subgroups based on ethnicity and cancer type. Based on cancer type, no significantly increased cancer risk was observed in any cancer (Figure 5A-E). However, a significant correlation with increased cancer risk was observed among Asians under 4 genetic models [T versus C (allele model): OR=1.30; 95% CI=1.07-1.58; CT+TT versus CC (dominant model): OR=1.30; 95% CI=1.02-1.64; TT versus CC (homozygote model): OR=2.23; 95% CI=1.23-4.05, TT versus CC+CT (recessive model): OR=2.07; 95% CI=1.15-3.72]. In contrast, no significant association was found between rs12826786 and cancer risk among Caucasians (Figure 5F-J). Sensitivity analysis indicated that these data were highly stable (Figure 6), and funnel plot, Begg's and Egger's tests indicated no publication bias (Figure 7). In addition, we found that there was no significant association between the *HOTAIR* rs4759314 A>G, rs1899663 G>T or rs874945 G>A polymorphism and cancer risk under all 5 models (Supplementary Table 2).

Discussion

Aberrant expression of lncRNAs is associated with cancer development [5]. *HOTAIR* has been recently investigated as potential connection to cancer susceptibility, and it has been widely reported as a functional lncRNA, expressed from the developmental *HOX*C locus and participated in multiple cancers [4-7,18,19,21,52,53]. Appearing evidence has indicated that polymorphisms of *HOTAIR* may modulate the susceptibility to cancer [26-30,32,33,36-42,54]. Moreover, several SNPs of lncRNAs identified to be involved in carcinogenesis have been reported to be associated with cancer risk [55,56]. In this meta-analysis, we pooled a total of 21 studies containing adequate sample size to verify further connections between *HOTAIR* polymorphisms rs920778 C>T, rs12826786 C>T, rs4759314 A>G, rs1899663 G>T or rs874945 G>A and increased risk for cancer.

The *HOTAIR* gene is located on the long arm of chromosome 12 (12q13.13). *HOTAIR* rs920778 polymorphism is located on intron 2 of the *HOTAIR* gene, which occurs as a result of substituting cytosine to thymine (C→T) and it has a genotype-specific effect on *HOTAIR* expression, which results in a higher *HOTAIR* expression among T allele carriers. As our expectation, distribution of *HOTAIR* rs920778 C>T had a significant association with cancer risk. Interestingly, our data indicated that rs920778 variants had a great influence on increasing cancer risk among Asians, and we also found that T allele or TT genotype of rs920778 strongly indicated a much higher risk of digestive cancer. Moreover, a significant correlation between T allele or TT genotype of rs920778 and gynecologic cancer had been found. This observation strongly suggests that *HOTAIR* rs920778 polymorphism could serve as a marker for digestive and gynecologic cancer risk evaluation in Asian populations. As for rs12826786 C>T, which is located in the promoter region of *HOTAIR*, a significant higher level of *HOTAIR* was observed in subjects carry-

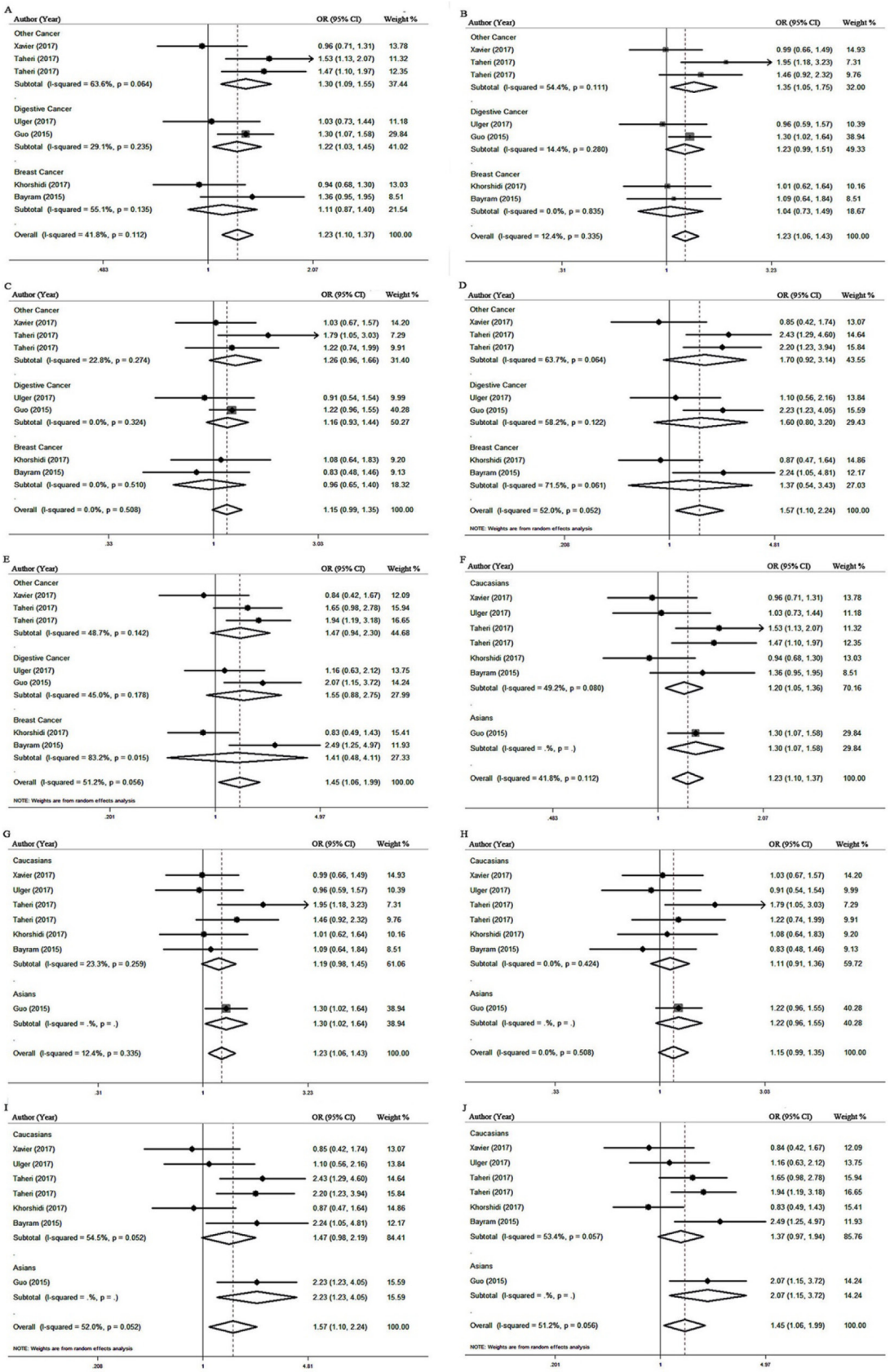

Figure 5. Forest plot of cancer risk in different cancer types and ethnicities associated with HOTAIR polymorphism rs12826786 under different models. Models represented **A:** allele model based on cancer types; **B:** dominant model based on cancer types; **C:** heterozygote model based on cancer types; **D:** homozygote model based on cancer types; **E:** recessive model based on cancer types; **F:** allele model based on ethnicities; **G:** dominant model based on ethnicities; **H:** heterozygote model based on ethnicities; **I:** homozygote model based on ethnicities; **J:** recessive model based on ethnicities.

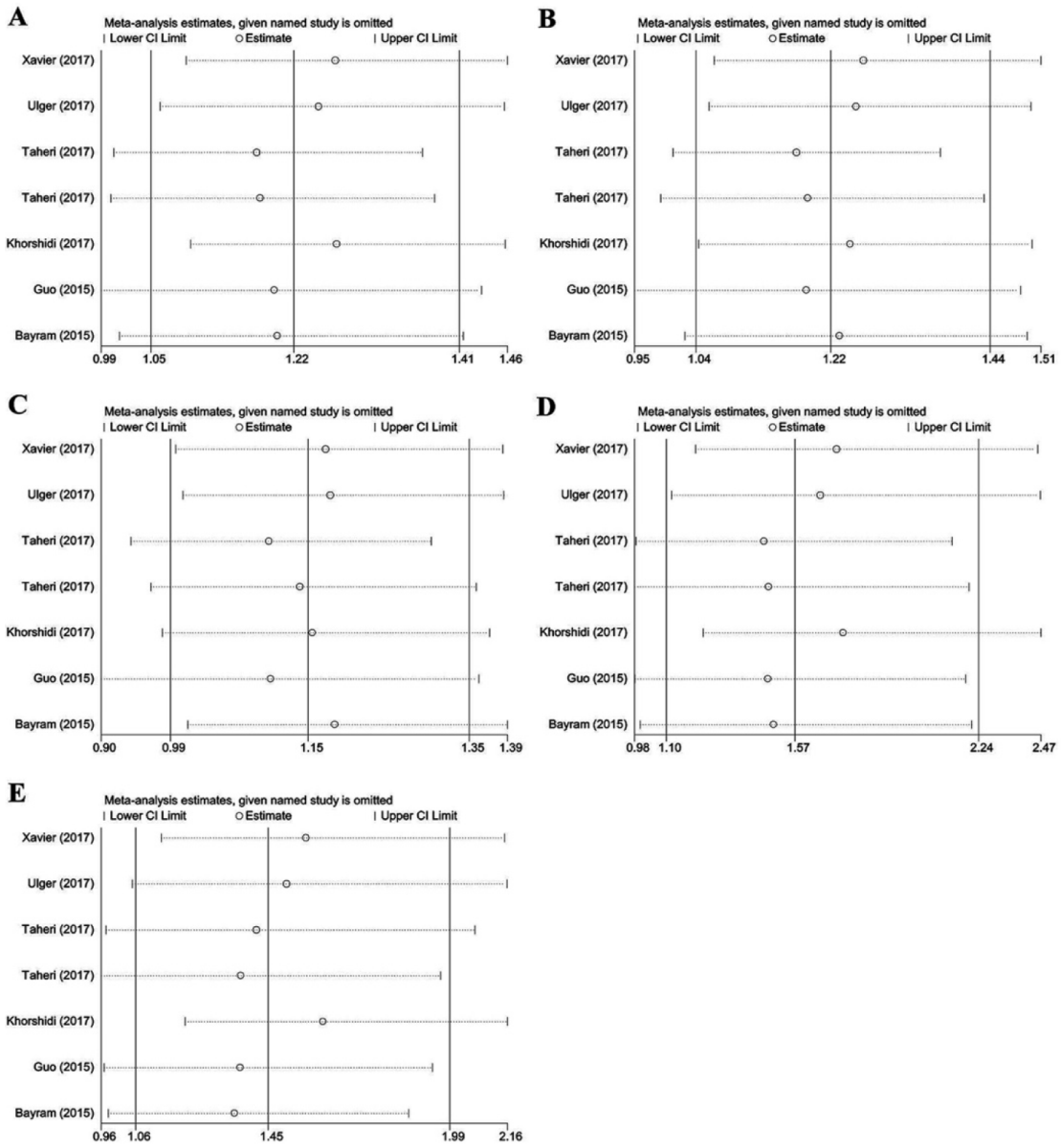

Figure 6. Sensitivity analysis for rs128268786 in this meta-analysis. There figures show the influence of individual studies on the summary OR in different models. The middle vertical axis indicates the overall OR and the two vertical axes indicate the 95% CI. Open circles indicate the pooled OR when 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. Models represented **A:** allele model; **B:** dominant model; **C:** heterozygote model; **D:** homozygote model; **E:** recessive model.

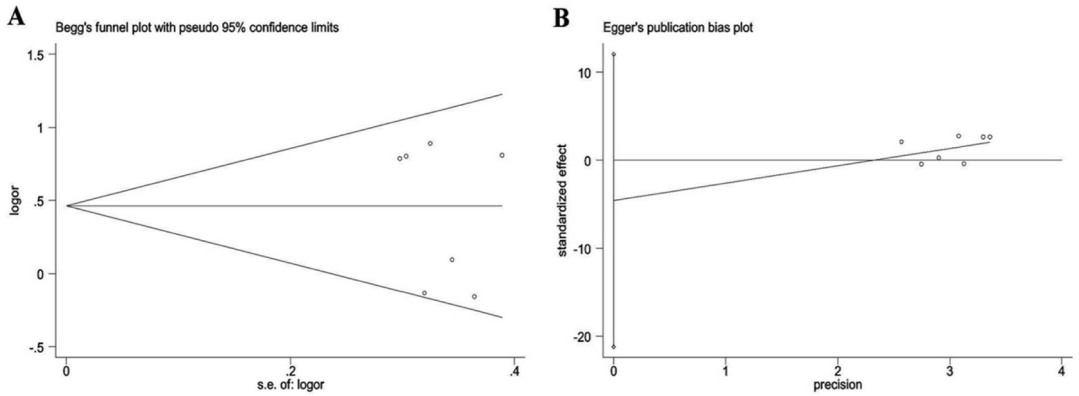

Figure 7. Begg's funnel plot and Egger's plot for publication bias for rs12826786. Each point represents a separate study for the indicated association. **A:** Begg's funnel plot; **B:** Egger's publication bias plot.

ing rs12826786 TT genotype than those with CC genotype in normal and gastric cardia adenocarcinoma tumor tissues, indicating C to T transition may influence the *HOTAIR* transcription and finally influence the expression of the gene [31]. However, Xavier-Magalhaes et al. [41] concluded that no statistically significant differences were found in the genotype or allele distributions of either rs920778 or rs12826786 between glioma patients and controls, suggesting these SNPs are not associated with glioma risk. In our studies, distribution of *HOTAIR* rs12826786 C>T had a significant association with cancer risk under the allele model, dominant model, homozygote model and recessive model. According to the subgroup analysis based on ethnicity, the association between rs12826786 variants and cancer risk was only observed in Asians. In subgroup analysis by cancer type, no risk was found to be linked with rs12826786 polymorphism. The difference between our studies and other published studies may be due to the fact that patients or controls came from different areas. For rs920778 and rs12826786 polymorphisms, the results of this meta-analysis were consistent with the functional assay. All this evidence indicates that lncRNA *HOTAIR* can act as an oncogene and increased *HOTAIR* expression might result in malignant transformation of normal cells.

To our knowledge, this is the first report to comprehensively assess the association between *HOTAIR* polymorphisms under 5 genetic models and cancer risk. Sufficient number of cases and controls were pooled from different studies and provided a more accurate estimation of the associations between the *HOTAIR* polymorphisms and cancer risk. We observed a significantly increased risk of cancer for the *HOTAIR* rs920778 C>T and rs12826786 polymorphisms, which are consistent with previous published studies [26-29,32,33,36,37,39,40,42]. Furthermore, subgroup analyses indicated that individuals with the T allele or TT genotype had a significantly increased cancer risk in Asian populations, suggesting that the increased cancer risk may be ethno-specific. Our data also indicated that rs920778 variants exhibit great correlation with cancer risk in digestive and gynecologic cancers. As for rs12826786, no significant association was observed in any cancer, but under the dominant model, homozygote model and recessive model, T allele or TT genotype may serve as an important factor in promoting the process of breast cancer. In contrast, a negative correlation was observed in the rs1899663 G>T, rs4759314 A>G and rs874945 G>A polymorphism analysis.

However, some limitations of this study still exist. First, although the analysis was performed with strict criteria for study inclusion and precise data extraction, significant heterogeneity between studies existed in some comparisons. Unfortunately, we did not perform meta-regression analysis which is not suitable for assessing heterogeneity with a sample size less than 10 [57]. Considering that the difference of ethnic diversity, study design, sample sizes, and the measurement of NOS error may contribute to common sources of heterogeneity [58], we performed subgroup analyses to explore the source of heterogeneity. For rs920778 and rs12826786, the heterogeneity of results did reduce but not eliminate based on subgroup analyses, indicating that all the above factors should be taken into consideration. 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. 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.

In conclusion, this meta-analysis provided evidence that the T allele or TT genotype of *HOTAIR* polymorphisms may serve as a potential genetic marker for cancer risk, especially in digestive, gynecologic and breast cancer patients among Asians.

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Conflict of interests

The authors declare no conflict of interests.

Supplementary Table 1. Genotype distributions of selected HOTAIR polymorphisms

rs920778	*CC genotype*		*CT genotype*		*TT genotype*		*P for HWE in controls*
Study	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	
Xavier (2017)	82	90	71	84	24	25	0.04
Qiu (2017)	235	580	69	78	25	52	<0.05
Zhu (2016)	1257	1465	960	841	183	94	0.05
Qiu (2016)	90	226	78	150	47	54	<0.05
Pan (2016)	420	980	321	575	59	45	<0.05
Guo (2016)	269	448	189	235	52	30	0.91
Bayram (2015)	40	41	52	66	31	15	0.14
Yan (2015)	12	18	151	190	339	296	0.06
Bayram (2015)	32	66	52	105	20	38	0.74
Zhang (2014)	1091	1323	826	749	181	78	<0.05
rs4759314	*AA genotype*		*AG genotype*		*GG genotype*		*P for HWE in controls*
Study	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	
Taheri (2017)	86	163	32	81	7	6	0.27
Taheri (2017)	85	163	54	81	6	6	0.27
Khorshidi (2017)	96	148	24	49	2	3	0.64
Jin (2017)	1012	1162	158	140	4	2	0.29
Hu (2017)	333	325	75	82	8	9	0.17
Hassanzarei (2017)	205	221	15	7	0	1	<0.05
Zhu (2017)	540	553	58	45	2	2	0.30
Pan (2016)	451	732	48	255	1	13	0.45
Guo (2016)	378	544	121	158	11	11	0.90
Yan (2015)	451	448	50	54	1	2	0.78
Xue (2015)	1011	1037	135	157	1	9	0.47
Guo (2015)	1528	1608	200	236	5	11	0.59
Du (2015)	1083	1464	186	172	6	8	0.23
Zhang (2014)	917	910	81	89	2	1	0.44
rs1899663	*GG genotype*		*GT genotype*		*TT genotype*		*P for HWE in controls*
Study	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	
Taheri (2017)	35	77	70	133	22	40	0.16
Taheri (2017)	57	77	73	133	13	40	0.16
Khorshidi (2017)	36	75	64	87	22	38	0.16
Hassanzarei (2017)	83	24	121	199	16	8	<0.05
Zhu (2017)	422	413	151	175	7	12	0.18
Pan (2016)	376	608	118	368	6	24	<0.05
Guo (2016)	356	509	146	191	8	13	0.31
Yan (2015)	339	326	149	158	14	20	0.88
Zhang (2014)	725	724	256	250	19	26	0.43
rs12826786	*CC genotype*		*CT genotype*		*TT genotype*		*P for HWE in controls*
Study	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	
Taheri (2017)	84	94	77	84	16	21	0.73
Ulger (2017)	38	73	47	99	20	35	0.88
Taheri (2017)	26	83	70	125	32	42	0.66
Taheri (2017)	36	83	66	125	40	42	0.66
Khorshidi (2017)	37	61	59	90	26	49	0.17
Hassanzarei (2017)	17	45	80	122	123	61	0.25
Guo (2015)	285	403	500	232	30	19	<0.05
Bayram (2015)	42	44	51	64	30	14	0.20
rs874945	*GG genotype*		*GA genotype*		*AA genotype*		*P for HWE in controls*
Study	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	
Wang (2017)	388	372	150	170	28	25	0.33
Jin (2017)	745	852	383	394	43	43	0.77

HWE: Hardy-Weinberg equilibrium

Supplementary Table 2. Summary ORs of the HOTAIR polymorphism and cancer risk

Variables	*n*	*Sample*	*Allele model*			*Dominant model*			*Heterozygote model*			*Homozygote model*			*Recessive model*		
		sizes	*OR(95%CI)*	*P*[a]	I^2(%)	*OR(95%CI)*	*P*[a]	I^2(%)	*OR(95%CI)*	*P*[a]	I^2(%)	*OR(95%CI)*	*P*[a]	I^2(%)	*OR(95%CI)*	*P*[a]	I^2(%)
rs920778	10	16,265	1.44(1.31,1.57)	0.000	58.0	1.45(1.36,1.55)	0.000	43.2	1.32(1.23,1.42)	0.000	35.9	2.35(2.05,2.69)	0.000	44.5	1.97(1.62,2.39)	0.000	56.7
Ethnicity																	
Asians	7	15,330	1.50(1.38,1.63)	0.000	48.8	1.49(1.39,1.59)	0.000	27.3	1.35(1.26,1.45)	0.000	17.9	2.52(2.21,2.95)	0.000	0.0	2.09(1.70,2.57)	0.000	55.6
Caucasians	3	934	1.10(0.91,1.33)	0.344	0.0	1.00(0.76,1.32)	0.978	0.0	0.92(0.69,1.23)	0.574	0.0	1.30(0.87,1.92)	0.196	12.7	1.39(0.84,2.94)	0.199	46.9
Cancer type																	
Digestive cancer[b]	3	6,961	1.40(1.23,1.60)	0.000	49.6	1.44(1.31,1.59)	0.000	0.0	1.31(1.19,1.45)	0.000	0.0	2.61(2.11,3.24)	0.000	72.0	2.08(1.33,3.27)	0.001	72.8
Breast cancer	2	1,251	1.36(1.13,1.64)	0.001	0.0	1.19(0.77,1.83)	0.426	0.0	0.93(0.59,1.46)	0.751	0.0	1.91(1.12,3.24)	0.017	0.0	1.69(1.08,2.64)	0.020	44.9
Gynecol cancer[c]	3	2,877	1.73(1.38,2.15)	0.000	63.4	1.69(1.44,1.99)	0.000	59.6	1.49(1.25,1.78)	0.000	64.4	2.57(1.93,3.43)	0.000	0.0	2.27(1.72,3.00)	0.000	0.0
Other cancer[d]	2	5,176	1.22(0.89,1.69)	0.231	77.1	1.38(1.24,1.54)	0.000	70.7	1.30(1.16,1.46)	0.000	59.2	2.04(1.60,2.59)	0.000	79.2	1.58(0.87,2.86)	0.129	70.9
rs12826786	8	3,645	1.22(1.05,1.41)	0.009	41.8	1.22(1.04,1.44)	0.017	12.4	1.15(0.99,1.35)	0.076	0.0	1.57(1.10,2.24)	0.013	52.0	1.45(1.06,1.99)	0.020	51.2
Ethnicity																	
Asians	1	1,169	1.30(1.07,1.58)	0.008	-	1.30(1.02,1.64)	0.030	-	1.22(0.96,1.55)	0.109	-	2.23(1.23,4.05)	0.008	-	2.07(1.15,3.72)	0.015	-
Caucasians	7	2,476	1.19(0.99,1.43)	0.058	49.2	1.19(0.95,1.48)	0.126	23.3	1.11(0.90,1.36)	0.333	0.0	1.47(0.98,2.19)	0.060	54.5	1.37(0.97,1.94	0.076	53.4
Cancer type																	
Digestive cancer[b]	2	1,481	1.20(0.97,1.49)	0.093	29.1	1.21(0.94,1.55)	0.133	14.4	1.16(0.93,1.44)	0.191	0.0	1.60(0.80,3.20)	0.188	58.2	1.55(0.88,2.75)	0.129	45.0
Breast cancer	3	1,018	1.12(0.78,1.60)	0.538	-55.1	1.04(0.73,1.49)	0.812	-0.0	0.96(0.65,1.40)	0.827	-0.0	1.37(0.54,3.43)	0.508	71.5	1.41(0.48,4.11)	0.530	-83.2
Other cancer[d]	3	1,146	1.30(0.97,1.73)	0.078	63.6	1.38(0.94,2.04)	0.103	54.4	1.27(0.93,1.74)	0.1381	22.8	1.70(0.92,3.14)	0.092	63.7	1.47(0.94,2.30)	0.095	48.7
rs4759314	14	22,671	0.97(0.79,1.18)	0.726	83.6	0.96(0.78,1.19)	0.712	89.3	0.96(0.78,1.19)	0.0.709	83.2	0.97(0.63,1.48)	0.473	21.4	0.98(0.65,1.48)	0.922	17.0
Ethnicity																	
Asians	10	21,145	0.93(0.73,1.17)	0.520	87.9	0.93(0.72,1.19)	0.556	88.1	0.94(0.73,1.20)	0.602	87.3	0.79(0.47,1.33)	0.378	26.5	0.80(0.49,1.31)	0.386	19.1
Caucasians	4	1,526	1.10(0.85,1.42)	0.487	20.3	1.07(0.75,1.53)	0.714	44.2	1.04(0.68,1.59)	0.844	55.8	1.69(0.83,3.47)	0.150	0.0	1.71(0.84,3.50)	0.138	0.0
Cancer type																	
Digestive cancer[b]	5	14,327	0.79(0.52,1.19)	0.259	93.3	0.79(0.50,1.23)	0.290	93.6	0.80(0.52,1.25)	0.328	93.3	0.47(0.19,1.20)	0.113	43.2	0.49(0.21,1.17)	0.108	35.9
Breast cancer	3	1,779	0.95(0.68,1.33)	0.782	22.0	0.99(0.64,1.52)	0.966	42.5	1.03(0.63,1.69)	0.903	53.4	0.69(0.19,2.58)	0.584	0.0	0.71(0.19,2.66)	0.615	0.0
Gynecol cancer[c]	2	3,780	1.21(1.03,1.43)	0.021	0.0	1.22(1.02,1.46)	0.290	93.6	1.21(1.01,1.44)	0.042	0.0	1.58(0.74,3.37)	0.237	0.0	1.54(0.72,3.28)	0.262	0.0
Other cancer[d]	4	2,785	1.08(0.90,1.30)	0.411	10.0	1.06(0.84,1.34)	0.605	84.1	1.04(0.80,1.34)	0.787	36.0	1.40(0.78,2.53)	0.263	0.0	1.41(0.79,2.54)	0.247	0.0
rs1899663	9	11,620	0.85(0.72,1.00)	0.046	75.5	0.77(0.58,1.03)	0.076	87.5	0.79(0.58,1.06)	0.115	88.0	0.73(0.56,0.95)	0.021	9.3	0.82(0.63,1.06)	0.132	19.1
Ethnicity																	
Asians	5	10,077	0.84(0.69,1.04)	0.107	79.4	0.83(0.64,1.08)	0.1651	82.9	0.85(0.66,1.10)	0.225	82.5	0.65(0.46,0.92)	0.016	0.0	0.68(0.48,0.96)	0.027	0.0
Caucasians	4	1,543	0.88(0.63,1.17)	0.331	77.2	0.68(0.29,1.59)	0.377	92.2	0.69(0.28,1.72)	0.431	92.8	0.81(0.48,1.37)	0.435	50.9	1.00(0.61,1.64)	0.987	56.2
Cancer type																	
Digestive cancer[b]	2	5,105	0.75(0.44,1.26)	0.270	93.0	0.72(0.37,1.37)	0.315	94.4	0.73(0.38,1.42)	0.356	94.3	0.60(0.35,1.04)	0.067	12.8	0.65(0.39,1.06)	0.085	0.0
Breast cancer	3	1,779	0.85(0.61,1.18)	0.323	78.2	0.63(0.23,1.73)	0.368	94.6	0.63(0.21,1.90)	0.410	95.1	0.83(0.53,1.30)	0.422	5.7	1.06(0.59,1.92)	0.841	52.5
Gynecol cancer[c]	1	1,223	1.05(0.84,1.31)	0.654		1.08(0.84,1.38)	0.548		1.09(0.85,1.41)	0.494		0.88(0.36,2.14)	0.778		0.86(0.35,2.09)	0.736	
Other cancer[d]	3	1,970	0.85(0.69,1.08)	0.200	50.2	0.85(0.65,1.10)	0.207	32.1	0.87(0.71,1.06)	0.168	0.0	0.69(0.36,1.33)	0.270	55.5	0.74,0.45,1.22)	0.238	34.7
rs874945	2	3690	1.04(0.92,1.17)	0.531	41.2	1.03(0.90,1.19)	0.630	60.5	1.02(0.89,1.18)	0.747	65.9	1.12(0.79,1.57)	0.527	0.0	1.11(0.79,1.56)	0.535	0.0

[a]P for heterogeneity (a random-effects model was used when the P value for heterogeneity test was < 0.05; otherwise, a fixed-effect model was used). [b]including gastric cancer, esophageal squamous cell carcinoma, colorectal cancer and gastric cardia adenocarcinoma. [c]including ovarian cancer and cervical cancer. [d]including glioma, papillary thyroid carcinoma, prostate cancer, benign prostate hyperplasia, pancreatic cancer and noise-induced hearing loss.

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