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REVIEW ARTICLE

Genetic association between *HOTAIR* gene and the risk of cancer: an updated meta-analysis

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Abstract. Several recent investigations show that HOX transcript antisense intergenic RNA (*HOTAIR*) play an important role in the pathogenesis of different cancers. *HOTAIR* polymorphisms has been widely studied in the context of association between with the risk of cancer pathogenesis. However, there is no certain conclusion about the role of *HOTAIR* polymorphisms in different cancer initiation and progression. Our team has selected eligible studies up to 1 May 2019, from several electronic databases, including Web of Science, PubMed, Scopus, and Google Scholar databases. We have included total number of 102 case–control investigations extracted from 41 eligible articles for the current meta-analysis. We calculated pooled odds ratio (ORs) with their corresponding 95% confidence intervals (CIs) using either fixed-effect or random-effect models for quantitative evaluation of the strength for the association between *HOTAIR* gene polymorphisms and the risk of cancer. Our current meta-analysis investigation showed that *HOTAIR* rs4759314 polymorphism particularly increased the overall risk of cancer in different models including homozygous, recessive and allele genetic. *HOTAIR* rs920778 significantly raised the cancer risk only in recessive genetic model. *HOTAIR* rs12826786 polymorphism was associated with cancer development in heterozygous, homozygous, dominant, recessive and allele genetic models. Also, an increase in cancer risk was observed with rs874945 polymorphism of *HOTAIR* gene in heterozygous, dominant and allele genetic models. The rs12427129 polymorphism showed correlation with cancer susceptibility only in recessive model. Subgroup analysis based on cancer type suggested that rs4759314 polymorphism significantly increased the risk of gastric and cervical cancers, and the rs920778 polymorphism increased the risk of gastrointestinal, cervical and gastric cancers. In summary, this study found that *HOTAIR* polymorphisms are significantly associated with cancer development.

Keywords. HOX transcript antisense intergenic RNA; polymorphism; cancer; meta-analysis.

Introduction

Cancer is considered as the second most common cause of mortality worldwide, resulting in about 9.6 million deaths in 2018 (Bray *et al.* 2018). One in six deaths is due to cancer. It has been estimated that the cancer-related deaths will reach about 13 million in 2030 (Bray *et al.* 2012). The precise

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†We dedicate this article to Prof. Mohamad Hashemi who passed away recently after the submission of this work. He was a pioneer in genetic studies.

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mechanism of cancer onset and development is not yet clear. Accumulating evidence suggests that cancer development is affected by both genetic and environmental factors (Hashemi *et al.* 2019a; Moazeni-Roodi *et al.* 2019a, b). Among the genetic risk factors, DNA polymorphism, especially single nucleotide polymorphism (SNP), is involved in the disease onset and development (Hashemi *et al.* 2019a, b, 2020).

Alteration in expression of long non-coding RNA (lncRNA) has been reported in several different types of human cancers (Mercer *et al.* 2009; Gibb *et al.* 2011; Prensner and Chinnaiyan 2011). LncRNA is the main class of nonprotein-coding RNA molecules with more than 200 nucleotides in length that plays a critical role in a various biological processes via regulation of gene expression in different levels (Erdmann *et al.* 2000; Mercer *et al.* 2009; Ponting *et al.* 2009; Lipovich *et al.* 2010; Wang and Chang 2011). Thus, the regulation of any biological process is affected by these lncRNAs. They can function as either oncogenes or tumour suppressor genes depending on the function of their target genes (Ji *et al.* 2019; Qu *et al.* 2019).

HOTAIR is one of the most well-known lncRNAs which can be found in the HOMEOBOX C (HOXC) locus on chromosome 12q13.13 (Rinn *et al.* 2007). *HOTAIR* could be an oncogene in different types of cancers. Many investigations have shown that *HOTAIR* overexpression is a risk factor tumour poor prognosis of tumours while involved in their invasion and progression (Gupta *et al.* 2010; Wu *et al.* 2014; Qu *et al.* 2019).

Several epidemiological investigations have focussed on evaluation as how *HOTAIR* polymorphisms could be correlated to the risk of cancer development in different populations (Zhang *et al.* 2014; Bayram *et al.* 2015a, b; Du *et al.* 2015; Guo *et al.* 2015; Xue *et al.* 2015; Yan *et al.* 2015; Bayram *et al.* 2016; Guo *et al.* 2016; Qiu *et al.* 2016; Wu *et al.* 2016; Zhou *et al.* 2016; Zhu *et al.* 2016; Hassanzarei *et al.* 2017; Hu *et al.* 2017; Jiang *et al.* 2017; Khorshidi *et al.* 2017; Li *et al.* 2017; Qiu *et al.* 2017; Ulger *et al.* 2017; Xavier-Magalhaes *et al.* 2017; Cui *et al.* 2018; Dadas and Aydin 2018; Elamir *et al.* 2018; Jiang *et al.* 2018; Lin *et al.* 2018; Oliveira *et al.* 2018; Su *et al.* 2018; Weng *et al.* 2018; Wu *et al.*, 2018; Yang *et al.* 2018; Jiang *et al.* 2019; Moschovis *et al.* 2019; Tung *et al.* 2019; Zhang *et al.* 2019); however, there are controversies in the results. The current study aims to provide a comprehensive view and a precise estimate on the possible role of *HOTAIR* rs4759314 A>G, rs920778 C>T, rs1899663 G>T, rs12826786 C>T, rs7958904 G>C, rs874945 G>A, rs12427129 G>A and rs10783618 C>T polymorphisms in cancer development using an updated meta-analysis of available publications.

Methods

Literature search

A systematic literature search on several electronic databases, including PubMed, Web of Science, Scopus and Google Scholar was conducted to identify all potentially eligible studies up to 1 May 2019, on the association between *HOTAIR* polymorphisms and cancer susceptibility. 'Cancer or carcinoma or tumour or neoplasms', 'Hox transcript antisense intergenic RNA or HOTAIR' and 'polymorphism or mutation or variant' were the keywords used in the aforementioned search engines. Moreover, relevant studies that were cited by the extracted publications were also collected.

Inclusion and exclusion criteria

The process of selecting eligible articles for the meta-analysis has been illustrated in figure 1. Studies that fulfil the following inclusion criteria were enrolled in the meta-analysis: original case–control studies investigating the association between *HOTAIR* polymorphisms and cancer susceptibility; studies published in English; studies with adequate genotypes data of *HOTAIR* polymorphisms in cases and controls. The exclusion criteria were studies with no genetic association of *HOTAIR* polymorphisms and cancer risk, conference abstracts, case reports, case-only studies, reviews, duplication publications, studies with insufficient published data, and unrelated studies.

Data extraction

We carefully evaluated the eligibility of the potential articles (independent evaluation of the articles by two of the coauthors of the manuscript). We have recorded the article's first author's family name, the year that the paper was published, the country that the research was carried out, ethnicity of the study population, source of control, cancer classification, number of cases and controls, genotypes and allele frequencies in cases and controls, and the *P* value for Hardy–Weinberg equilibrium (HWE) in control group.

Statistical analysis

Meta-analysis was carried out using STATA (v14.0, Stata Corporation, USA). The association strength of *HOTAIR* polymorphisms with cancer was assessed by calculating pooled odds ratio (ORs) and corresponding 95% confidence intervals (95% CIs). Z-test was carried out to assess the statistical significance of pooled ORs, where $P < 0.05$ denoted a statistically significant OR. The heterogeneity among the included publications was evaluated using Cochran's Q-test and the I^2 test. A *P*-value less than 0.10 indicated heterogeneity among studies. For cases with heterogeneity, ORs were obtained using a random effects model. A fixed-effects model was employed for other cases. Publication bias was assessed using both Begg's funnel plot and Egger's test. A *P*-value less than 0.05 reflected statistically notable publication bias.

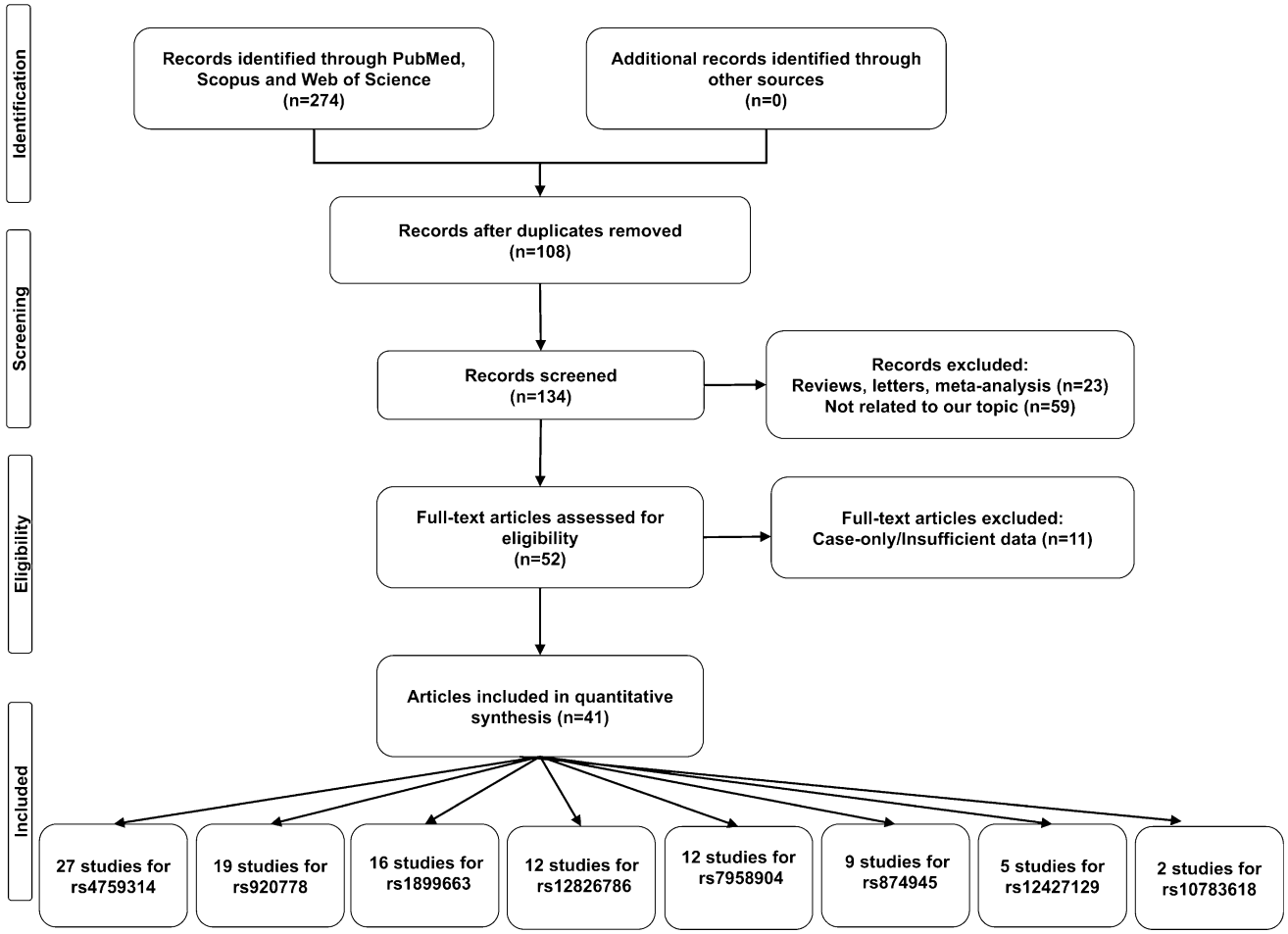

Figure 1. Flow chart illustrating the study selection process used in this meta-analysis. We have summarized the process and criteria of the article selection in our investigation to use them for current meta-analysis study.

We have investigated the consistency of results to evaluate the sensitivity of the analysis. We excluded the studies that included the pooled-analysis to measure the effect of the distinct data on the pooled OR.

Results

Study characteristics

The study retrieval and selection process of the eligible articles for the meta-analysis are summarized in figure 1. The total number of 102 case–control studies from 41 published articles (Zhang *et al.* 2014; Bayram *et al.* 2015a, b; Du *et al.* 2015; Guo *et al.* 2015; Xue *et al.* 2015; Yan *et al.* 2015; Bayram *et al.* 2016; Guo *et al.* 2016; Qiu *et al.* 2016; Wu *et al.* 2016; Zhou *et al.* 2016; Zhu *et al.* 2016; Hassanzarei *et al.* 2017; Hu *et al.* 2017; Jiang *et al.* 2017; Khorshidi *et al.* 2017; Li *et al.* 2017; Qiu *et al.* 2017; Ulger *et al.* 2017; Xavier-Magalhaes *et al.* 2017; Cui *et al.* 2018; Dadas and Aydin 2018; Elamir *et al.* 2018; Jiang *et al.* 2018; Lin *et al.* 2018; Oliveira *et al.* 2018; Su *et al.* 2018; Weng *et al.* 2018; Wu *et al.* 2018; Yang *et al.* 2018; Jiang *et al.* 2019; Moschovis *et al.* 2019; Tung *et al.* 2019; Zhang *et al.* 2019) satisfied the inclusion and exclusion criteria. Twenty-seven studies on rs4759314 (16,715 cases and 20,701 controls), 19 studies on rs920778 (10,763 cases and 14,130 controls), 16 studies on rs1899663 (7228 cases and 9723 controls), 12 studies on rs12826786 (2826 cases and 3945 controls), 12 studies on rs7958904 (10,206 cases and 12,105 controls), nine studies on rs874945 (6798 cases and 8410 controls), five studies on rs12427129 (3099 cases and 4330 controls), and two studies on rs10783618 (1947 cases and 2131 controls) were included in the meta-analysis (table 1).

Main analysis results

Table 2 summarizes the main results of this meta-analysis. The findings showed that *HOTAIR* rs4759314 significantly increased the risk of overall cancer in homozygous (OR = 1.34, 95% CI = 1.12–1.60, $P = 0.001$, GG vs AA), recessive (OR = 1.34, 95% CI = 1.29–1.09, $P = 0.004$, GG vs AG + AA) and allele (OR = 1.10, 95% CI = 1.00–1.20,

Table 1. Characteristics of all studies included in the meta-analysis.

Author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	Cases					Controls					HWE (*P*)
								AA	AG	GG	A	G	AA	AG	GG	A	G	
rs4759314																		
Du M.	2015	China	Asian	Gastric cancer	HB	TaqMan	1275/1644	1083	186	6	2352	198	1464	172	8	3100	188	0.230
Guo W.	2015	China	Asian	Gastric cancer	HB	PCR-RFLP	515/654	461	53	1	975	55	589	64	1	1242	66	0.587
Guo L.	2016	China	Asian	Cervical cancer	HB	MALDI-TOF	510/713	378	121	11	877	143	544	158	11	1246	180	0.903
Hassanzarei S.	2017	Iran	Asian	Breast cancer	PB	PCR-RFLP	220/229	205	15	0	425	15	221	7	1	449	9	0.002
Hu P.	2017	China	Asian	Pancreatic cancer	PB	TaqMan	416/416	333	75	8	741	91	325	82	9	732	100	0.166
Jiang D.	2019	China	Asian	Pancreatic cancer	HB	MALDITOF	900/900	733	148	19	1614	186	791	103	6	1685	115	0.195
Jin H.	2017	China	Asian	Cervical cancer	HB	TaqMan	1174/1304	1012	158	4	2182	166	1162	140	2	2464	144	0.294
Khorshidi H. R.	2017	Iran	Asian	Breast cancer	HB	ARMS-PCR	122/200	96	24	2	216	28	148	49	3	345	55	0.641
Li H.	2017	China	Asian	HCC	HB	MALDI-TOF	482/520	315	147	20	777	187	356	149	15	861	179	0.901
Li H.	2018	China	Asian	Lung cancer	PB	TaqMan	543/551	526	16	1	1068	18	489	61	1	1039	63	0.527
Lin Y.	2018	China	Asian	Breast cancer	PB	Sequencing	969/970	801	157	11	1759	179	817	144	9	1778	162	0.348
Moschovis D.	2019	Greece	Caucasian	Pancreatic cancer	PB	PCR-RFLP	111/125	81	25	5	187	35	100	24	1	224	26	0.735
Pan W.	2016	China	Asian	Gastric cancer	HB	PCR-RFLP	500/1000	451	48	1	950	50	914	83	3	1911	89	0.448
Su S. C.	2018	Taiwan	Asian	Oral cancer	PB	TaqMan	907/1200	759	139	9	1657	157	1009	184	7	2202	198	0.656
Taheri M.	2017	Iran	Asian	Prostate cancer	HB	ARMS-PCR	125/250	86	32	7	204	46	163	81	6	407	93	0.268
Tung M. C.	2019	Taiwan	Asian	Urothelial cell carcinoma	HB	TaqMan	431/862	363	67	1	793	69	727	128	7	1582	142	0.604
Wang C.	2018	China	Asian	Lung cancer	HB	TaqMan	262/451	238	21	3	497	27	412	37	2	861	41	0.246
Wang X.	2018	China	Asian	Bladder cancer	HB	TaqMan	1045/1394	897	129	19	1923	167	1217	143	34	2577	211	<0.001
Weng S. L.	2018	Taiwan	Asian	Cervical cancer	HB	TaqMan	116/318	95	21	0	211	21	266	48	4	580	56	0.284
Wu H.	2016	China	Asian	Epithelial Ovarian cancer	HB	TaqMan	1000/1000	819	140	41	1778	222	852	125	23	1829	171	<0.001
Wu B.	2018	China	Asian	HNSCC	PB	TaqMan	366/731	113	188	65	414	318	268	362	101	898	564	0.224
Xue Y.	2014	China	Asian	Colorectal cancer	HB	TaqMan	1733/1855	1528	200	5	3256	210	1608	236	11	3452	258	0.467
Yan R.	2015	China	Asian	Breast cancer	PB	PCR-RFLP	502/504	451	50	1	952	52	448	54	2	950	58	0.785
Yang X.	2018	China	Asian	Neuroblastoma	HB	TaqMan	391/810	325	63	3	713	69	698	105	7	1501	119	0.175
Zhang X.	2014	China	Asian	ESCC	HB	PCR-RFLP	1000/1000	917	81	2	1915	85	910	89	1	1909	91	0.436
Zhou Q.	2016	China	Asian	Osteosarcoma	HB	TaqMan	500/500	423	62	15	908	92	425	64	11	914	86	<0.001
Zhu H.	2016	China	Asian	PTC	NA	PCR-RFLP	600/600	540	58	2	1138	62	553	45	2	1151	49	0.297
								CC	CT	TT	C	T	CC	CT	TT	C	T	
rs920778																		
Bayram S.	2015	Turkey	Caucasian	Breast cancer	HB	TaqMan	123/122	31	52	40	114	132	15	66	41	96	148	0.140
Bayram S.	2015	Turkey	Caucasian	Gastric cancer	HB	TaqMan	104/209	20	52	32	92	116	38	105	66	181	237	0.738
Guo L.	2016	China	Asian	Cervical cancer	HB	MALDI-TOF	510/713	269	189	52	727	293	448	235	30	1131	295	0.907
Hassanzarei S.	2017	Iran	Asian	Breast Cancer	PB	PCR-RFLP	220/231	33	119	68	185	255	8	98	125	114	348	0.032
Li H.	2017	China	Asian	HCC	HB	MALDI-TOF	482/520	248	186	48	682	282	304	180	36	788	252	0.191
Li H.	2018	China	Asian	Lung cancer	PB	TaqMan	543/551	22	197	324	241	845	22	203	326	247	855	0.164
Oliveira A. I.	2018	Portugal	Caucasian	Prostate cancer	PB	PCR-RFLP	151/180	23	50	78	96	206	27	72	81	126	234	0.105
Pan W.	2016	China	Asian	Gastric cancer	HB	PCR-RFLP	800/1600	420	321	59	1161	439	980	575	45	2535	665	<0.001
Qiu H.	2016	China	Asian	Cervical cancer	HB	TaqMan	215/430	90	78	47	258	172	226	150	54	602	258	<0.001
Qiu H.	2017	China	Asian	Ovarian Cancer	HB	TaqMan	329/680	235	69	25	539	119	580	78	22	1238	122	<0.001
Su S. C.	2018	Taiwan	Asian	Oral cancer	PB	TaqMan	907/1200	64	403	440	531	1283	73	513	614	659	1741	0.011
Tung M. C.	2019	Taiwan	Asian	Urothelial carcinoma	HB	TaqMan	431/862	38	176	217	252	610	55	360	447	470	1254	0.119

Table 1 (*contd*)

								CC	CT	TT	C	T	CC	CT	TT	C	T	
Wang C.	2018	China	Asian	Lung cancer	HB	TaqMan	262/451	110	132	20	352	172	233	192	26	658	244	0.095
Weng X.	2018	Taiwan	Asian	Cervical cancer	HB	TaqMan	116/318	9	50	57	68	164	19	134	165	172	464	0.226
Xavier-Magalhaes A.	2017	Portugal	Caucasian	Glioma	PB	PCR-RFLP	177/199	82	71	24	235	119	90	84	25	264	134	0.438
Yan R.	2015	China	Asian	Breast cancer	PB	PCR-RFLP	502/504	12	151	339	175	829	18	190	296	226	782	0.060
Yang X.	2018	China	Asian	Neuroblastoma	HB	TaqMan	393/810	44	158	191	246	540	70	310	430	450	1170	0.189
Zhang X.	2014	China	Asian	ESCC	HB	PCR-RFLP	2098/2150	1091	826	181	3008	1188	1323	749	78	3395	905	0.025
Zhu H.	2016	China	Asian	PTC	NA	PCR-RFLP	2400/2400	1257	960	183	3474	1326	1465	841	94	3771	1029	0.048
								GG	GT	TT	G	T	GG	GT	TT	G	T	
rs1899663																		
Dadas E.	2018	Turkey	Caucasian	NSCLC	HB	TaqMan	87/93	39	37	11	115	59	41	40	12	122	64	0.649
Guo L.	2016	China	Asian	Cervical cancer	HB	MALDI-TOF	510/713	356	146	8	858	162	509	191	13	1209	217	0.308
Hassanzarei S.	2017	Iran	Asian	Breast cancer	PB	PCR-RFLP	220/231	83	121	16	287	153	24	199	8	247	215	<0.001
Khorshidi H. R.	2017	Iran	Asian	Breast cancer	HB	ARMS-PCR	122/200	36	64	22	136	108	75	87	38	237	163	0.161
Li H.	2017	China	Asian	HCC	HB	MALDI-TOF	482/520	334	136	12	804	160	367	142	11	876	164	0.524
Lin Y.	2018	China	Asian	Breast cancer	PB	Sequencing	969/970	628	299	42	1555	383	665	284	21	1614	326	0.142
Pan W.	2016	China	Asian	Gastric cancer	HB	PCR-RFLP	500/1000	376	118	6	870	130	732	255	13	1719	281	0.078
Su S. C.	2018	Taiwan	Asian	Oral cancer	PB	TaqMan	907/1200	575	294	38	1444	370	773	395	32	1941	459	0.026
Taheri M.	2017	Iran	Asian	Prostate cancer	HB	ARMS-PCR	127/250	35	70	22	140	114	77	133	40	287	213	0.165
Tung M. C.	2019	Taiwan	Asian	Urothelial carcinoma	HB	TaqMan	431/862	265	148	18	678	184	550	285	27	1385	339	0.172
Wang C.	2018	China	Asian	Lung cancer	HB	TaqMan	262/451	178	66	18	422	102	254	189	8	697	205	<0.001
Weng X.	2018	Taiwan	Asian	Cervical cancer	HB	TaqMan	116/318	74	38	4	186	46	209	101	8	519	117	0.302
Yan R.	2015	China	Asian	Breast cancer	PB	PCR-RFLP	502/504	339	149	14	827	177	326	158	20	810	198	0.876
Yang X.	2018	China	Asian	Neuroblastoma	HB	TaqMan	393/811	242	128	23	612	174	511	274	26	1296	326	0.139
Zhang X.	2014	China	Asian	ESCC	HB	PCR-RFLP	1000/1000	725	256	19	1706	294	724	250	26	1698	302	0.430
Zhu H.	2016	China	Asian	PTC	NA	PCR-RFLP	600/600	442	151	7	1035	165	413	175	12	1001	199	0.184
								CC	CT	TT	C	T	CC	CT	TT	C	T	
rs12826786																		
Bayram S.	2016	Turkey	Caucasian	Breast cancer	HB	TaqMan	123/122	42	51	30	135	111	44	64	14	152	92	0.197
Dadas E.	2018	Turkey	Caucasian	NSCLC	HB	TaqMan	87/93	33	41	13	107	67	38	41	14	117	69	0.593
Guo W.	2015	China	Asian	GCA	HB	PCR-RFLP	515/654	285	200	30	770	260	403	232	19	1038	270	0.034
Hassanzarei S.	2017	Iran	Asian	Breast cancer	PB	PCR-RFLP	220/228	17	80	123	114	326	45	122	61	212	244	0.254
Khorshidi H. R.	2017	Iran	Asian	Breast cancer	HB	ARMS-PCR	122/200	37	59	26	133	111	61	90	49	212	188	0.171
Li H.	2018	China	Asian	Lung cancer	PB	TaqMan	543/551	340	185	18	865	221	381	156	14	918	184	0.677
Oliveira A. I.	2018	Portugal	Caucasian	Prostate cancer	PB	PCR-RFLP	151/180	85	51	15	221	81	88	71	21	247	113	0.258
Taheri M.	2017	Iran	Asian	Prostate cancer	HB	ARMS-PCR	128/250	26	70	32	122	134	83	125	42	291	209	0.662
Ulger Y.	2017	Turkey	Asian	Gastric cancer	HB	TaqMan	105/207	38	47	20	123	87	73	99	35	245	169	0.884
Wang C.	2018	China	Asian	Lung cancer	HB	TaqMan	262/451	200	49	13	449	75	355	85	11	795	107	0.036
Xavier-Magalhaes A.	2017	Portugal	Caucasian	Glioma	PB	PCR-RFLP	177/199	84	77	16	245	109	94	84	21	272	126	0.730
Yang X.	2018	China	Asian	Neuroblastoma	HB	TaqMan	393/810	240	127	26	607	179	507	275	28	1289	331	0.209
								GG	CG	CC	G	C	GG	CG	CC	G	C	
rs7958904																		
Cui P.	2018	China	Asian	Breast cancer	PB	TaqMan	1489/1675	881	505	103	2267	711	986	583	106	2555	795	0.115
Du M.	2015	China	Asian	Gastric cancer	HB	TaqMan	739/1057	412	276	51	1100	378	568	404	85	1540	574	0.271

Table 1 (*contd*)

								GG	CG	CC	G	C	GG	CG	CC	G	C	
Elamir A.	2018	Egypt	African	Gastric cancer	HB	TaqMan	25/25	6	9	10	21	29	15	10	0	40	10	0.211
Jiang D.	2018	China	Asian	Pancreatic cancer	HB	MALDI-TOF	400/400	215	156	29	586	214	237	136	27	610	190	0.221
Jin H.	2017	China	Asian	Cervical cancer	HB	TaqMan	1153/1292	640	427	86	1707	599	735	494	63	1964	620	0.083
Lin Y.	2018	China	Asian	Breast cancer	PB	Sequencing	969/970	489	396	84	1374	564	537	373	60	1447	493	0.655
Wang X.	2018	China	Asian	Bladder cancer	HB	TaqMan	1042/1392	551	400	91	1502	582	764	531	97	2059	725	0.718
Wu H.	2016	China	Asian	Epithelial ovarian	HB	TaqMan	1000/1000	594	355	51	1543	457	533	380	87	1446	554	0.105
Wu B.	2018	China	Asian	HNSCC	PB	TaqMan	366/732	140	167	59	447	285	241	369	122	851	613	0.336
Xue Y.	2014	China	Asian	Colorectal cancer	HB	TaqMan	1731/1852	1019	605	107	2643	819	992	704	156	2688	1016	0.052
Yang X.	2018	China	Asian	Neuroblastoma	HB	TaqMan	392/810	192	154	46	538	246	431	310	69	1172	448	0.215
Zhou Q.	2016	China	Asian	Osteosarcoma	HB	TaqMan	900/900	524	320	56	1368	432	466	346	88	1278	522	0.046
								GG	GA	AA	G	A	GG	GA	AA	G	A	
rs874945																		
Du M.	2015	China	Asian	Gastric cancer	HB	TaqMan	751/1057	495	225	31	1215	287	714	307	36	1735	379	0.672
Elamir A.	2018	Egypt	African	Gastric cancer	HB	TaqMan	25/25	6	5	14	17	33	15	8	2	38	12	0.539
Jin H.	2017	China	Asian	Cervical cancer	HB	TaqMan	1171/1289	745	383	43	1873	469	852	394	43	2098	480	0.757
Wang X.	2018	China	Asian	Bladder cancer	HB	TaqMan	1048/1396	649	370	29	1668	428	931	416	49	2278	514	0.764
Wu H.	2016	China	Asian	Epithelial ovarian cancer	HB	TaqMan	1000/1000	665	283	52	1613	387	677	279	44	1633	367	0.029
Wu B.	2018	China	Asian	HNSCC	PB	TaqMan	365/730	191	152	22	534	196	358	317	55	1033	427	0.183
Xue Y.	2014	China	Asian	Colorectal Cancer	HB	TaqMan	1147/1202	751	356	40	1858	436	817	346	39	1980	424	0.749
Yang X.	2018	China	Asian	Neuroblastoma	HB	TaqMan	391/811	237	129	25	603	179	506	277	28	1289	333	0.183
Zhou Q.	2016	China	Asian	Osteosarcoma	HB	TaqMan	900/900	577	256	67	1410	390	608	243	49	1459	341	<0.001
								GG	AG	AA	G	A	GG	AG	AA	G	A	
rs12427129																		
Jiang D.	2019	China	Asian	Pancreatic cancer	HB	MALDI-TOF	400/400	359	36	5	754	46	356	41	3	753	47	0.143
Su S. C.	2018	Taiwan	Asian	Oral cancer	PB	TaqMan	907/1200	743	157	7	1643	171	975	221	4	2171	229	0.021
Tung M. C.	2019	Taiwan	Asian	Urothelial cancer	HB	TaqMan	431/862	350	76	5	776	86	691	167	4	1549	175	0.068
Weng S. L.	2018	Taiwan	Asian	Cervical cancer	HB	TaqMan	116/318	96	19	1	211	21	275	42	1	592	44	0.649
Zhang J.	2019	China	Asian	HCC	PB	MassARRAY	1245/1550	1012	210	23	2234	256	1219	309	22	2747	353	0.632
								CC	CT	TT	C	T	CC	CT	TT	C	T	
rs10783618																		
Guo	2015	China	Asian	GCA	HB	PCR-RFLP	515/654	262	212	41	736	294	365	249	40	979	329	0.775
Jiang	2017	China	Asian	Breast cancer	PB	iPLEX	1432/1486	769	546	117	2084	780	816	553	117	2185	787	0.088

Table 2. The pooled ORs and 95% CIs for the association between *HOTAIR* polymorphisms and susceptibility to cancer.

			Association test			Heterogeneity			Publication bias tests	
Polymorphism	Number	Genetic model	OR (95% CI)	Z	*P*	χ2	I^2 (%)	*P*	Egger's test *P* value	Begg's test *P* value
rs4759314	27	AG vs AA	1.08 (0.98–119)	1.53	0.126	61.04	57.4	0.000	0.214	0.307
		GG vs AA	1.34 (1.12–1.60)	3.19	0.001	23.73	0.0	0.591	0.540	0.400
		AG + GG vs AA	1.09 (0.99–1.21)	1.80	0.071	64.14	59.5	0.000	0.237	0.370
		GG vs AG + AA	1.29 (1.09–1.54)	2.87	0.004	22.96	0.0	0.635	0.755	0513
		G vs A	1.10 (1.00–1.20)	2.01	0.044	66.53	60.9	0.000	0.227	0.416
rs920778	19	CT vs CC	1.11 (0.97–1.27)	1.57	0.116	54.91	67.2	0.000	0.004	0.002
		TT vs CC	1.25 (0.92–1.71)	1.41	0.157	141.30	87.3	0.000	0.022	0.046
		CT + TT vs CC	1.14 (0.98–1.32)	1.66	0.096	81.78	78.0	0.000	0.004	0.003
		TT vs CT + CC	1.30 (1.04–1.62)	2.31	0.021	148.27	87.9	0.000	0.325	0.248
		T vs C	1.14 (0.99–1.30)	1.89	0.059	166.57	89.2	0.000	0.098	0.248
rs1899663	16	GT vs GG	0.91 (0.78–1.06)	1.24	0.215	68.62	78.1	0.000	0.215	0.368
		TT vs GG	1.20 (0.95–1.51)	1.54	0.123	24.28	32.8	0.060	0.118	0.126
		GT + TT vs GG	0.83 (0.81–1.08)	0.97	0.334	62.84	76.1	0.000	0.181	0.150
		TT vs GT + GG	1.25 (0.99–1.58)	1.87	0.061	26.40	43.2	0.034	0.550	0.322
		T vs G	0.99 (0.91–1.08)	0.21	0.832	31.60	52.5	0.007	0.281	0.126
rs12826786	12	CT vs CC	1.12 (1.01–1.25)	2.07	0.039	13.11	16.1	0.286	0.766	0.681
		TT vs CC	1.61 (1.15–2.24)	2.79	0.005	31.17	64.7	0.001	0.358	0.411
		CT + TT vs CC	1.19 (1.02–1.39)	2.19	0.028	21.36	48.5	0.030	0.862	0.337
		TT vs CT + CC	1.51 (1.11–2.05)	2.66	0.008	32.86	66.5	0.001	0.055	0.493
		T vs C	1.22 (1.04–1.43)	2.47	0.014	39.91	72.4	0.000	0.545	0.217
rs7958904	12	CG vs GG	0.96 (0.89–1.05)	0.89	0.371	21.86	49.7	0.025	0.223	0.170
		CC vs GG	1.00 (0.78–1.29)	0.03	0.976	58.5	81.2	0.000	0.616	0.938
		CG + CC vs GG	1.15 (0.94–1.40)	1.34	0.181	135.66	91.9	0.000	0.103	0.028
		CC vs CG + GG	1.02 (0.81–1.27)	0.13	0.893	48.11	77.1	0.000	0.689	0.815
		C vs G	1.00 (0.90–1.12)	0.06	0.952	69.21	84.1	0.000	0.101	0.131
rs874945	9	AG vs GG	1.10 (1.02–1.18)	2.55	0.011	6.54	0.0	0.587	0.646	0.211
		AA vs GG	1.22 (0.95–1.57)	1.57	0.115	17.74	54.9	0.023	0.076	0.825
		AG + AA vs GG	1.11 (1.04–1.19)	3.04	0.002	11.00	27.3	0.202	0.264	0.677
		AA vs AG + GG	1.20 (0.93–1.54)	1.43	0.154	18.30	56.3	0.019	0.070	0.677
		A vs G	1.11 (1.01–1.22)	2.10	0.035	20.69	61.3	0.008	0.039	0.677
rs12427129	5	AG vs GG	0.89 (0.78–1.00)	1.89	0.059	2.44	0.0	0.655	0.191	0.327
		AA vs GG	1.56 (0.99–2.47)	1.90	0.057	1.54	0.0	0.820	0.070	0.624
		AG + AA vs GG	0.92 (0.81–1.03)	1.42	0.157	2.43	0.0	0.658	0.127	0.327
		AA vs AG + GG	1.60 (1.01–2.53)	2.02	0.043	1.41	0.0	0.842	0.081	0.624
		A vs G	0.95 (0.85–1.07)	0.81	0.415	2.25	0.0	0.689	0.088	0.327
rs10783618	2	CT vs CC	1.09 (0.95–1.24)	1.24	0.215	0.72	0.0	0.397	–	–
		TT vs CC	1.16 (0.89–1.51)	1.08	0.278	1.17	14.3	0.280	–	–
		CT + TT vs CC	1.10 (0.96–1.26)	1.38	0.169	1.15	13.0	0.284	–	–
		TT vs CT + CC	1.11 (0.88–1.40)	0.88	0.379	0.83	0.0	0.364	–	–
		T vs C	1.09 (0.96–1.24)	1.34	0.182	1.47	31.9	0.226	–	–

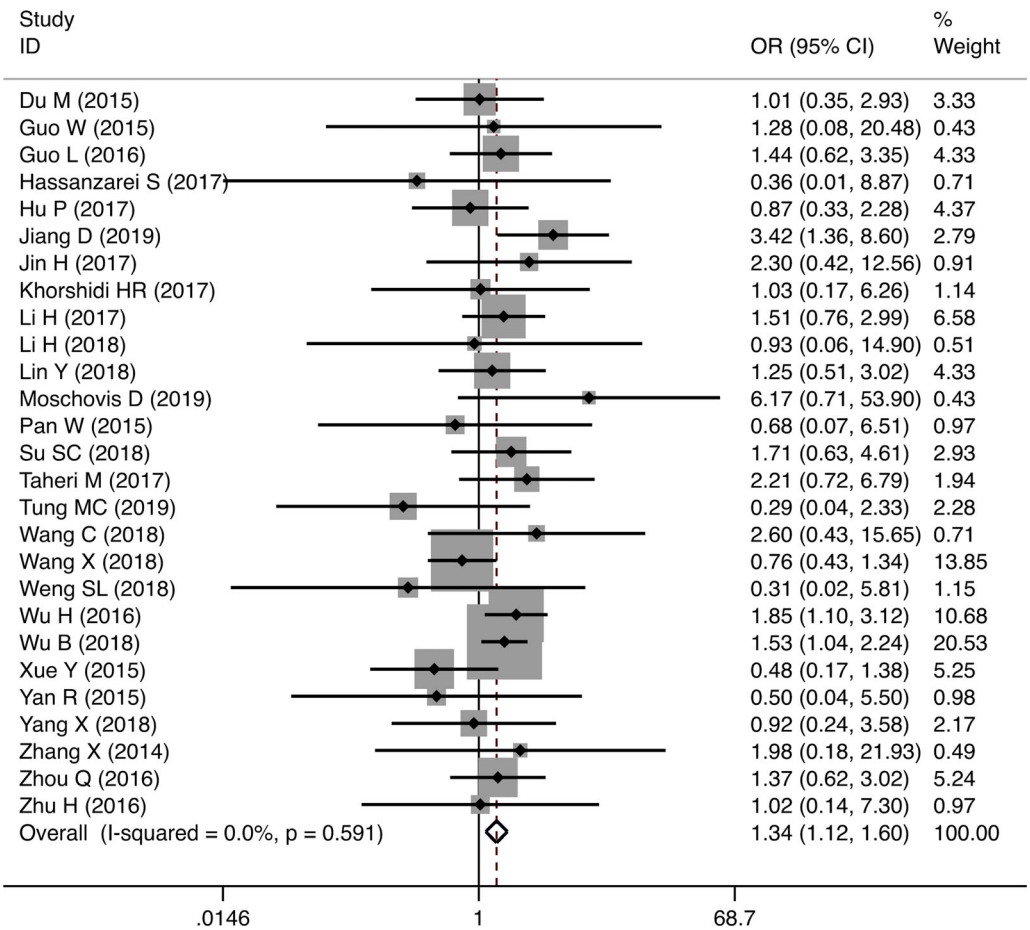

Figure 2. Forest plot of ORs and 95% CIs for the association between the rs4759314 polymorphism and overall cancer susceptibility for GG vs AA. We identified the weight and the significance of each study in our meta-analysis. The middle dot in each line shows the odd ratio (OR) and the size of the box shows the weight of each study in meta-analysis (larger box shows more weight).

$P = 0.044$, G vs A) genetic models (table 2; figure 2). The *HOTAIR* rs920778 polymorphism elevated the risk of cancer only in recessive genetic model (OR = 1.30, 95% CI = 1.04–1.62, $P = 0.021$, TT vs CT + CC). A statistically noticeable increase in the risk of cancer was found with the *HOTAIR* rs12826786 polymorphism in heterozygous (OR = 1.12, 95% CI = 1.01–1.25, $P = 0.039$, CT vs CC), homozygous (OR = 1.61, 95% CI = 1.15–2.24, $P = 0.005$, TT vs CC), dominant (OR = 1.19, 95% CI = 1.02–1.39, $P = 0.028$, CT + TT vs CC), recessive (OR = 1.51, 95% CI = 1.11–2.05, $P = 0.008$, TT vs CT + CC) and allele (OR = 1.22, 95% CI = 1.04–1.43, $P = 0.014$, T vs C) genetic models. The rs874945 polymorphism of *HOTAIR* gene notably increased the risk of cancer in heterozygous (OR = 1.10, 95% CI = 1.02–1.18, $P = 0.0211$, AG vs GG), dominant (OR = 1.11, 95% CI = 1.04–1.19, $P = 0.002$, AG + AA vs GG) and allele (OR = 1.11, 95% CI = 1.01–1.22, $P = 0.035$, A vs G) genetic models. The rs12427129 polymorphism only elevated cancer risk in recessive (OR = 1.60, 95% CI = 1.01–2.53, $P = 0.043$, AA vs AG + GG) genetic model. No significant association was found between the rs7958904, rs1899663 and rs10783618 polymorphisms of *HOTAIR* gene and cancer susceptibility.

Subgroup analysis results

We performed subgroup analysis based on the ethnicity and the type of cancer (table 3). We have been able to show that that rs4759314 polymorphism increased the risk of cancer in Asian population (OR = 1.33, 95% CI = 1.11–1.60, $P = 0.002$, GG vs AA; OR = 1.27, 95% CI = 1.07–1.52, $P = 0.007$, GG vs AG + AA). Stratified analysis by cancer type showed that the rs4759314 polymorphism significantly increased the risk of gastric cancer (OR = 1.31, 95% CI = 1.10–1.55, $P = 0.002$, AG vs AA; OR = 1.31, OR = 1.30, 95% CI = 1.10–1.53, $P = 0.002$, AG + GG vs AA; OR = 1.26, 95% CI = 1.07–1.48, $P = 0.004$, G vs A) and cervical cancer (OR = 1.21, 95% CI = 1.02–1.43, $P = 0.031$, AG vs AA; OR = 1.21, 95% CI = 1.02–1.44, $P = 0.025$, AG + vs AA; OR = 1.20, 95% CI = 1.02–1.40, $P = 0.025$, G vs A). We also showed that there was no significant connotation

Table 3. Stratified analysis.

			Association test			Heterogeneity			Publication bias tests	
Polymorphism	Number	Genetic model	OR (95% CI)	Z	*P*	χ2	I^2 (%)	*P*	Egger's test *P* value	Begg's test *P* value
rs4759314 A > G										
Asian	26	AG vs AA	1.08 (0.97–1.19)	1.43	0.152	60.82	58.9	0.000	0.163	0.179
		GG vs AA	1.33 (1.11–1.60)	3.02	0.002	21.83	0.0	0.646	0.309	0.197
		AG + GG vs AA	1.09 (0.98–1.20)	1.66	0.097	63.30	60.5	0.000	0.152	0.193
		GG vs AG + AA	1.27 (1.07–1.52)	2.69	0.007	21.09	21.09	0.687	0.489	0.298
		G vs A	1.09 (0.99–1.19)	1.83	0.067	64.80	61.4	0.000	0.126	0.193
GI cancer	9	AG vs AA	1.12 (0.96–1.32)	1.42	0.155	19.77	59.5	0.011	0.999	0.835
		GG vs AA	1.38 (0.96–1.98)	1.74	0.083	11.13	28.1	0.194	0.922	0.835
		AG + GG vs AA	1.14 (0.96–1.35)	1.49	0.136	24.05	66.7	0.002	0.862	1.000
		GG vs AG + AA	1.35(0.94–1.93)	1.61	0.108	10.38	22.9	0.239	0.907	1.000
		G vs A	1.15 (0.96–1.36)	1.54	0.123	27.80	71.2	0.001	0.775	0.677
Breast cancer	4	AG vs AA	1.05 (0.87–1.27)	0.52	0.602	4.83	37.9	0.185	0.932	1.000
		GG vs AA	1.02 (0.50–2.10)	0.06	0.955	0.95	0.0	0.814	0.283	0.117
		AG + GG vs AA	1.05 (0.87–1.27)	0.51	0.609	4.22	28.9	0.239	0.913	1.000
		GG vs AG + AA	1.02 (0.49–2.10)	0.05	0.961	0.95	0.0	0.814	0.350	0.117
		G vs A	1.04 (0.88–1.24)	0.49	0.625	3.49	13.9	0.323	0.988	1.000
Gastric cancer	3	AG vs AA	1.31 (1.10–1.55)	3.10	0.002	2.47	19.1	0.291	0.124	0.117
		GG vs AA	0.97 (0.39–2.39)	0.07	0.944	0.14	0.0	0.931	0.880	0.602
		AG + GG vs AA	1.30 (1.10–1.53)	3.03	0.002	2.35	15.0	0.308	0.097	0.117
		GG vs AG + AA	0.93 (0.38–2.30)	0.15	0.880	0.14	0.0	0.934	0.939	0.602
		G vs A	1.26 (1.07–1.48)	2.87	0.004	2.04	1.9	0.361	0.074	0.117
Pancreatic cancer	3	AG vs AA	1.22 (0.82–1.80)	0.98	0.326	6.02	66.8	0.049	0.800	0.602
		GG vs AA	2.20 (0.70–6.87)	1.35	0.176	5.25	61.9	0.072	0.723	0.602
		AG + GG vs AA	1.29 (0.83–2.00)	1.12	0.263	8.32	76.0	0.016	0.872	0.602
		GG vs AG + AA	2.11 (0.72–6.20)	1.36	0.173	4.73	57.7	0.094	0.712	0.602
		G vs A	1.33 (0.85–2.09)	1.24	0.215	10.66	81.2	0.005	0.937	0.602
Cervical cancer	3	AG vs AA	1.21 (1.02–1.43)	2.15	0.031	0.76	0.0	0.682	0.945	0.602
		GG vs AA	1.36 (0.67–2.75)	0.85	0.395	1.36	0.0	0.506	–	–
		AG + GG vs AA	1.21 (1.02–1.44)	2.24	0.025	0.78	0.0	0.679	0.735	0.602
		GG vs AG + AA	1.32 (0.65–2.68)	0.78	0.436	1.37	0.0	0.505	–	–
		G vs A	1.20 (1.02–1.40)	2.24	0.025	1.06	0.0	0.589	0.597	0.602
Lung cancer	2	AG vs AA	0.49 (0.12–1.93)	1.02	0.307	11.92	91.6	0.001	–	–
		GG vs AA	1.92 (0.42–8.66)	0.85	0.398	0.37	0.0	0.542	–	–
		AG + GG vs AA	0.52 (0.13–2.13)	0.91	0.365	13.48	0.0	0.9216	–	–
		GG vs AG + AA	1.97 (0.44–8.89)	0.88	0.378	0.31	0.0	0.577	–	–
		G vs A	0.56 (0.14–2.27)	0.81	0.420	14.58	93.1	0.000	–	–
rs920778 T > C										
Asian	15	CT vs CC	1.19 (1.05–1.36)	2.67	0.008	39.58	64.6	0.000	0.047	0.009
		TT vs CC	1.37 (0.96–1.95)	1.76	0.078	126.14	88.9	0.000	0.095	0.151
		CT + TT vs CC	1.22 (1.05–1.43)	2.53	0.011	64.38	78.3	0.000	0.038	0.012
		TT vs CT + CC	1.36 (1.05–1.76)	2.32	0.020	146.41	90.4	0.000	0.211	0.125
		T vs C	1.18 (1.02–1.37)	2.18	0.029	154.77	91.0	0.000	0.243	0.650

Table 3 (*contd*)

			Association test			Heterogeneity			Publication bias tests	
Polymorphism	Number	Genetic model	OR (95% CI)	Z	*P*	$\chi 2$	I^2 (%)	*P*	Egger's test *P* value	Begg's test *P* value
Caucasian	4	CT vs CC	0.78 (0.59–104)	1.69	0.090	4.81	37.6	0.187	0.373	0.089
		TT vs CC	0.88 (0.63–1.23)	0.73	0.465	3.53	15.1	0.316	0.035	0.174
		CT + TT vs CC	0.83 (0.64–1.09)	1.35	0.178	4.91	39.0	0.178	0.418	0.174
		TT vs CT + CC	1.09 (0.85–1.41)	0.67	0.503	1.14	0.0	0.767	0.354	0.497
		T vs C	0.97 (0.82–1.14)	0.39	0.695	3.10	3.2	0.376	0.316	0.174
GI cancers	4	CT vs CC	1.31 (1.19–1.44)	5.51	0.000	1.21	0.0	0.751	0.025	0.042
		TT vs CC	2.04 (1.31–3.18)	3.16	0.002	12.75	76.5	0.0005	0.145	0.042
		CT + TT vs CC	1.43 (1.30–1.56)	7.64	0.000	2.54	0.0	0.469	0.005	0.042
		TT vs CT + CC	1.83 (1.18–2.83)	2.71	0.007	14.64	79.5	0.002	0.217	0.042
		T vs C	1.36 (1.20–1.54)	55.6	0.080	6.75	55.6	0.080	0.023	0.042
Cervical cancer	3	CT vs CC	1.29 (1.06–1.58)	2.55	0.011	1.37	0.0	0.505	0.195	0.177
		TT vs CC	1.83 (0.96–3.48)	1.84	0.066	7.72	74.1	0.021	0.222	0.602
		CT + TT vs CC	1.44 (1.14–1.83)	3.06	0.002	2.65	24.5	0.266	0.257	0.117
		TT vs CT + CC	1.64 (0.88–3.07)	1.56	0.118	12.04	83.4	0.002	0.422	0.117
		T vs C	1.33 (0.98–1.79)	1.84	0.066	8.77	77.2	0.012	0.317	0.117
Breast cancer	3	CT vs CC	0.51 (0.22–1.18)	1.57	0.118	7.16	72.1	0.028	0.898	0.602
		TT vs CC	0.48 (0.11–2.01)	1.01	0.314	20.52	90.3	0.000	0.292	0.117
		CT + TT vs CC	0.51 (0.17–1.55)	1.19	0.232	13.77	85.5	0.001	0.851	0.602
		TT vs CT + CC	0.81 (0.34–1.96)	0.46	0.643	32.49	93.8	0.000	0.618	0.602
		T vs C	0.78 (0.38–1.58)	0.70	0.486	37.44	94.7	0.000	0.554	0.602
Gastric cancer	2	CT vs CC	1.27 (1.07–1.51)	2.75	0.006	0.93	0.0	0.334	–	–
		TT vs CC	1.74 (0.54–5.62)	0.92	0.358	8.73	88.5	0.003	–	–
		CT + TT vs CC	1.28 (0.88–1.85)	1.31	0.191	1.79	44.1	0.181	–	–
		TT vs CT + CC	1.65 (0.59–4.61	0.95	0.341	10.17	90.2	0.001	–	–
		T vs C	1.21 (0.82–1.79)	0.97	0.331	4.75	78.9	0.029	–	–
rs1899663 G > T										
Asian	15	GT vs GG	0.90 (0.77–1.06)	1.24	0.214	68.62	79.06	0.000	0.171	0.458
		TT vs GG	1.21 (0.95–1.54)	1.54	1.25	23.98	41.6	0.046	0.147	0.216
		GT + TT vs GG	0.93 (0.80–1.07)	0.96	0.335	62.84	77.7	0.000	0.147	0.181
		TT vs GT + GG	1.27 (0.99–1.62)	1.88	0.060	26.03	46.2	0.026	0.625	0.458
		T vs G	0.99 (0.91–1.08)	0.20	0.738	31.58	55.7	0.005	0.249	0.125
Breast cancer	4	GT vs GG	0.74 (0.38–1.43)	0.91	0.364	48.53	93.8	0.000	0.475	0.497
		TT vs GG	1.06 (0.58–1.95)	0.20	0.839	9.17	67.3	0.027	0.127	0.174
		GT + TT vs GG	0.75 (0.40–1.41)	0.90	0.369	47.41	93.7	0.000	0.411	0.174
		TT vs GT + GG	1.29 (0.74–2.24)	0.91	0.364	8.53	64.8	0.036	0.943	0.497
		T vs G	0.94 (0.69–1.27)	0.42	0.673	20.60	85.4	0.000	0.463	0.497
GI cancer	4	GT vs GG	0.99 (0.86–1.14)	0.12	0.901	0.83	0.0	0.662	0.905	0.602
		TT vs GG	0.75 (0.56–1.35)	0.62	0.536	0.90	0.0	0.636	0.513	0.602
		GT + TT vs GG	0.98 (0.86–1.12)	0.27	0.791	0.82	0.0	0.664	0.950	0.602
		TT vs GT + GG	0.87 (0.56–1.34)	0.63	0.530	0.89	0.0	0.640	0.473	0.602
		T vs G	0.98 (0.87–1.10)	0.41	0.681	0.83	0.0	0.660	0.809	0.602

Table 3 (*contd*)

			Association test			Heterogeneity			Publication bias tests	
Polymorphism	Number	Genetic model	OR (95% CI)	Z	*P*	$\chi 2$	I^2 (%)	*P*	Egger's test *P* value	Begg's test *P* value
Cervical cancer	2	GT vs GG	1.09 (0.87–1.36)	0.72	0.469	0.01	0.0	0.916	–	–
		TT vs GG	1.04 (0.50–2.13)	0.10	0.924	0.37	0.0	0.541	–	–
		GT + TT vs GG	1.08 (0.87–1.34)	0.71	0.480	0.00	0.0	0.975	–	–
		TT vs GT + GG	1.01 (0.49–2.06)	0.03	0.973	0.39	0.0	0.534	–	–
		T vs G	1.06 (0.88–1.29)	0.63	0.530	0.03	0.0	0.852	–	–
rs12826786										
Asian	8	CT vs CC	1.18 (1.04–1.33)	2.65	0.008	8.31	15.8	0.306	0.612	0.322
		TT vs CC	1.09 (1.29–2.80)	3.23	0.001	20.03	65.1	0.006	0.813	0.805
		CT + TT vs CC	1.29 (1.08–1.56)	2.74	0.006	14.96	53.2	0.037	0.373	0.322
		TT vs CT + CC	1.70 (1.19–2.43)	2.94	0.003	21.68	67.7	0.003	0.188	0.805
		T vs C	1.31 (1.09–1.58)	2.85	0.004	28.74	75.6	0.000	0.924	0.216
Caucasian	4	CT vs CC	0.91 (0.71–1.17)	0.72	0.474	1.64	0.0	0.651	0.773	0.497
		TT vs CC	1.10 (0.75–1.60)	0.48	0.629	5.00	40.0	0.172	0.751	0.497
		CT + TT vs CC	0.95 (0.75–1.20)	0.46	0.648	1.85	0.0	0.603	0.426	0.174
		TT vs CT + CC	1.15 (0.68–1.96)	0.53	0.596	6.50	53.8	0.090	0.834	0.497
		T vs C	1.01 (0.85–1.20)	0.11	0.913	4.55	34.1	0.208	0.633	0.497
Breast cancer	3	CT vs CC	1.14 (0.76–1.69)	0.63	0.529	2.96	32.5	0.228	0.500	0.602
		TT vs CC	2.19 (0.73–6.50)	1.41	0.160	15.75	87.3	0.000	0.933	0.602
		CT + TT vs CC	1.45 (0.76–2.75)	0.14	0.254	8.62	76.8	0.013	0.193	0.117
		TT vs CT + CC	1.94 (0.78–4.83)	1.43	0.153	17.59	88.6	0.000	0.690	0.602
		T vs C	1.48 (0.82–2.67)	1.29	0.197	20.66	90.3	0.000	0.541	0.602
Prostate cancer	2	CT vs CC	1.14 (0.48–2.70)	0.30	0.761	5.94	83.2	0.015	–	–
		TT vs CC	1.36 (0.42–4.36)	0.52	0.606	5.84	82.9	0.016	–	–
		CT + TT vs CC	1.19 (0.46–3.07)	0.37	0.715	8.08	87.6	0.004	–	–
		TT vs CT + CC	1.22 (0.63–2.38)	0.60	0.549	2.34	57.3	0.126	–	–
		T vs C	1.11 (0.59–2.10)	0.33	0.743	7.79	87.2	0.005	–	–
rs7958904 G > C										
China	11	CG vs GG	0.96 (0.88–1.04)	0.99	0.321	20.20	50.5	0.027	0.416	0.350
		CC vs GG	0.98 (0.77–1.24)	0.19	0.851	51.75	80.7	0.000	0.616	0.938
		CG + CC vs GG	1.11 (0.91–1.36)	1.04	0.229	129.61	92.3	0.000	0.108	0.73
		CC vs CG + GG	1.00 (0.81–1.23)	0.04	0.965	42.36	76.4	0.000	0.689	0.815
		C vs G	0.98 (0.88–1.08)	0.41	0.682	54.57	81.7	0.000	0.469	0.392
Breast cancer	2	CG vs GG	1.05 (0.88–1.26)	0.57	0.569	2.28	56.1	0.131	–	–
		CC vs GG	1.27 (0.91–1.78)	1.40	0.162	2.23	55.1	0.135	–	–
		CG + CC vs GG	1.09 (0.89–1.34)	0.81	0.416	3.23	69.0	0.072	–	–
		CC vs CG + GG	1.23 (0.95–1.60)	1.58	0.114	1.41	29.1	0.235	–	–
		C vs G	1.10 (0.92–1.31)	1.04	0.300	3.65	72.6	0.056	–	–
Gastric cancer	2	CG vs GG	1.13 (0.56–2.28)	0.35	0.724	1.67	40.0	0.197		
		CC vs GG	4.94 (0.08–292.08)	0.77	0.443	7.50	86.7	0.006	–	–
		CG + CC vs GG	1.87 (0.38–9.16)	0.77	0.442	6.80	85.3	0.009	–	–
		CC vs CG + GG	1.00 (0.71–1.41)	0.01	0.994	6.52	84.7	0.011	–	–
		C vs G	0.98 (0.84–1.13)	0.32	0.750	15.05	93.4	0.000	–	–

Table 3 (*contd*)

Polymorphism	Number	Genetic model	Association test			Heterogeneity			Publication bias tests	
			OR (95% CI)	Z	*P*	χ2	I^2 (%)	*P*	Egger's test *P* value	Begg's test *P* value
rs874945										
China		AG vs GG	1.09 (1.02–1.17)	2.52	0.012	6.31	0.0	0.504	0.017	0.026
		AA vs GG	1.06 (0.99–1.37)	1.84	0.066	8.71	19.6	0.274	0.768	0.458
		AG + AA vs GG	1.10 (1.03–1.18)	2.89	0.004	5.51	0.0	0.598	0.051	0.138
		AA vs AG + GG	1.14 (0.97–1.33)	1.57	0.116	9.16	23.6	0.241	0.874	0.711
		A vs G	1.09 (1.03–1.16)	3.01	0.003	5.74	0.0	0.571	0.314	0.621
GI cancer	3	AG vs GG	1.10 (0.96–1.25)	1.33	0.182	0.40	0.0	0.820	–	–
		AA vs GG	1.78 (0.78–4.08)	1.36	0.174	8.92	77.6	0.012	–	–
		AG + AA vs GG	1.17 (0.90–1.54)	1.16	0.244	5.56	64.0	0.062	–	–
		AA vs AG + GG	1.74 (0.77–3.97)	1.32	0.185	9.08	78.0	0.011	–	–
		A vs G	1.38 (0.94–2.01)	1.64	0.101	14.84	86.5	0.001	–	–
Gastric cancer	2	AG vs GG	1.07 (0.87–1.31)	0.61	0.545	0.27	0.0	0.605	–	–
		AA vs GG	4.06 (0.30–54.10)	1.06	0.289	8.14	87.7	0.004	–	–
		AG + AA vs GG	1.99 (0.48–8.36)	0.94	0.346	5.56	82.0	0.018	–	–
		AA vs AG + GG	3.72 (0.32–42.62)	1.06	0.291	8.15	87.7	0.004	–	–
		A vs G	2.44 (0.45–13.36)	1.03	0.304	14.65	93.2	0.000	–	–

between this polymorphism and possibility of gastrointestinal (GI) cancer, breast cancer, pancreatic cancer and lung cancer.

In case of the rs920778 polymorphism, our findings proposed a considerable increase in cancer risk among Asian population (OR = 1.19, 95% CI = 1.05–1.36, *P* = 0.008, CT vs CC; OR = 1.22, 95% CI = 1.05–1.43, *P* = 0.011, CT + TT vs CC; OR = 1.36, 95% CI = 1.05–1.76, *P* = 0.020, TT vs CT + CC; OR = 1.18, 95% CI = 1.02–1.367, *P* = 0.029, T vs C); however, no association was observed in Caucasian population. Further, this polymorphism significantly increased the risk of GI cancer (OR = 1.31, 95% CI = 1.19–1.44, *P* = 0.000, CT vs CC; OR = 2.04, 95% CI = 1.31–3.18, *P* = 0.002, TT vs CC; OR = 1.43, 95% CI = 1.30–1.56, *P* = 0.000, CT + TT vs CC; OR = 1.83, 95% CI = 1.18–2.83, *P* = 0.007, TT vs CT + CC), cervical cancer (OR = 1.29, 95% CI = 1.06–1.58, *P* = 0.011, CT vs CC; OR = 1.44, 95% CI = 1.14–1.83, CT + TT vs CC) and gastric cancer (OR = 1.27, 95% CI = 1.07–1.51, *P* = 0.006, CT vs CC). No association was noticed between this polymorphism and susceptibility to breast cancer was noticed.

The results showed that the rs1899663 polymorphism did not affect cancer susceptibility in Asian population. Subgroup analysis by cancer type also revealed that this polymorphism was not associated with the risk of breast cancer, GI cancer and cervical cancer.

We observed that the rs12826786 polymorphism notably raised the cancer risk in Asian population (OR = 1.18, 95% CI = 1.04–1.33, *P* = 0.008, CT vs CC; OR = 1.09, 95% CI = 1.29–2.80, *P* = 0.001, TT vs CC; OR = 1.29, 95% CI = 1.08–1.56, *P* = 0.006, TT vs CT + CC; OR = 1.70, 95% CI = 1.19–2.43, *P* = 0.003, TT vs CT + CC; OR = 1.31, 95% CI = 1.09–1.58, *P* = 0.004, T vs C), but not in Caucasians. Also, no risk of breast and prostate cancers was observed with this polymorphism.

The rs874945 polymorphism significantly elevated cancer risk in Chinese population (OR = 1.09, 95% CI = 1.02–1.17, *P* = 0.012, AG vs GG; OR = 1.10, 95% CI = 1.03–1.18, *P* = 0.004, AG + AA vs GG; OR = 1.09, 95% CI = 1.03–1.16, *P* = 0.003, A vs G).

Regarding the rs1899663 and rs7958904 polymorphisms, the results indicated no association with cancer susceptibility.

Heterogeneity and publication bias

The shapes of funnel plots were symmetric, and the *P*-values of Egger's tests revealed publication bias for the rs4759314, rs7958904, rs1899663, rs12826786 and rs12427129 polymorphisms in all genetic models (table 2; figure 3). For the rs920778 polymorphism, there was no publication bias in recessive and allele genetic models (table 2).

Sensitivity analysis

Sensitivity analysis was performed to evaluate the effect of individual studies on the consistency of the pooled ORs by excluding each data from the pooled analysis one by one in every genetic model.

For the rs4759314 variant, the pooled ORs with corresponding 95% CIs were not affected by excluding each individual study in homozygous and recessive genetic models (figure 4). Sensitivity analysis for rs920778 showed changes in the pooled ORs under all five genetic models (i.e. heterozygous, homozygous, dominant, recessive and allele). Regarding rs1899663, the pooled ORs with corresponding 95% CIs stayed consistent in heterozygous, homozygous, dominant and allele genetic models. For rs12826786, no single study significantly altered the pooled ORs with corresponding 95% CIs in homozygous, recessive and allele genetic models. For rs7958904, the pooled ORs with corresponding 95% CIs remained consistent in all genetic models after exclusion of each study. Sensitivity analysis for rs874945 resulted in no change in the pooled ORs with corresponding 95% CIs in recessive genetic model. For rs12427129, sensitivity analysis reported that the pooled ORs with corresponding 95% CIs were not altered notably by excluding each study in dominant and allele genetic models. However, according to the sensitivity analysis more studies should be considered in the meta-analysis to obtain more reliable results.

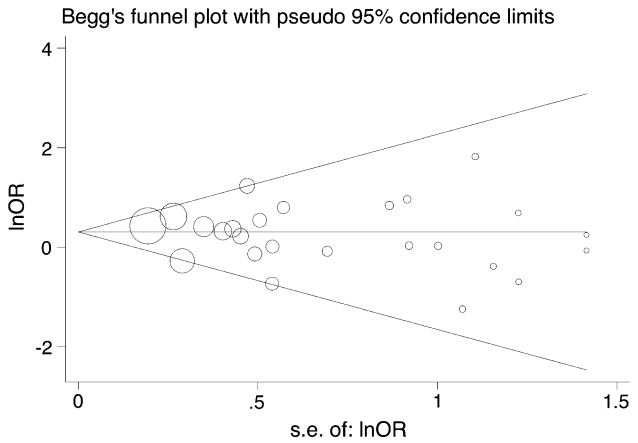

Figure 3. Begg's funnel plot for the association between the rs4759314 polymorphism and overall cancer susceptibility for GG vs AA. The horizontal line in the funnel plot indicates the estimate effect, while the sloping lines indicate the expected 95% CI.

Discussion

LncRNAs are considered to be involved in epigenetic, transcriptional, or posttranscriptional levels of various biological processes. Pathophysiological activities such as cell growth, invasion, apoptosis, metastasis and cancer development have been shown to be regulated by these molecules

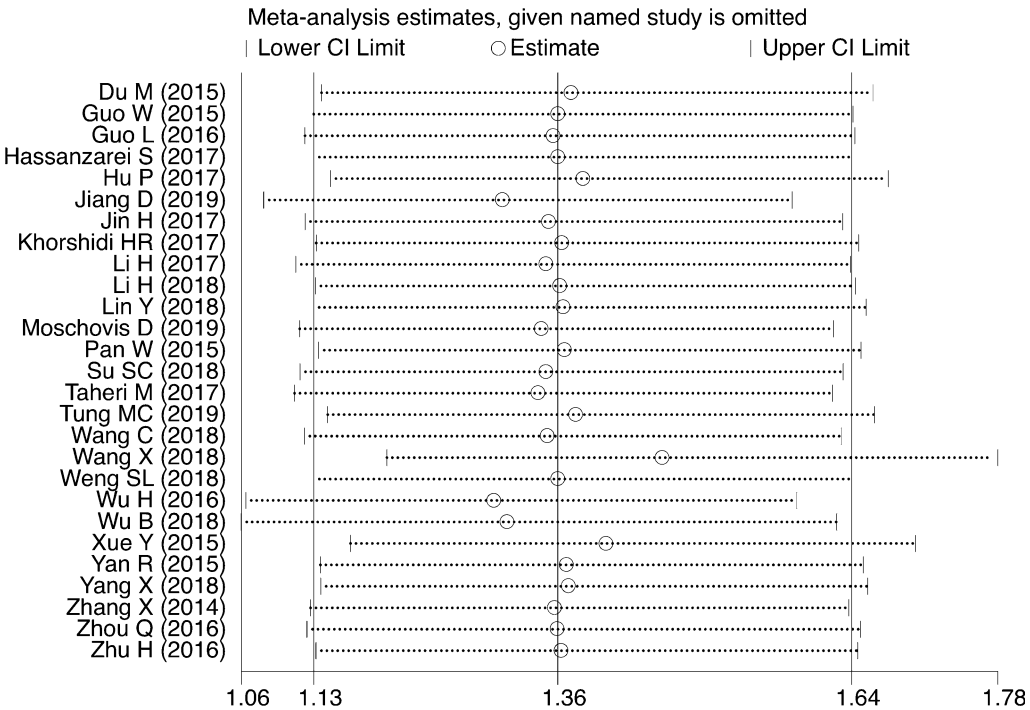

Figure 4. Sensitivity analyses between the rs4759314 polymorphism and overall cancer susceptibility for GG vs AA. We show the influence of individual studies on the summary OR in different models. The middle vertical axis indicates the overall OR and the two vertical axes indicate the 95% CI. Open circles indicate the pooled OR when the indicated study on the left is omitted from the meta-analysis.

(Mercer *et al.* 2009; Ponting *et al.* 2009; Wilusz *et al.* 2009; Gupta *et al.* 2010; Gutschner and Diederichs 2012; Qiu *et al.* 2013; Yoon *et al.* 2013; Zhang *et al.* 2013).

HOTAIR, a *trans*-acting lncRNA that acts as a molecular scaffold, exhibits pro-oncogenic activity in various cancers. Its overexpression may be implicated in several hallmarks of malignant transformation of normal cells, such as cellular proliferation, apoptosis inhibition, genomic instability, angiogenesis, invasion and metastasis (Tsai *et al.* 2010; Hajjari and Salavaty 2015; Xu *et al.* 2018). Several studies suggested that genetic variation may affect the function and expression of the relevant genes (Pastinen *et al.* 2006; Ryan *et al.* 2010).

In this meta-analysis, we pooled a total of 41 studies to assess the association of *HOTAIR* rs4759314 A>G, rs920778 C>T, rs1899663 G>T, rs12826786 C>T, rs7958904 G>C, rs874945 G>A, rs12427129 G>A and rs10783618 C>T polymorphisms with cancer susceptibility. Our meta-analysis proposed that rs4759314, rs920778, rs12826786, rs874945 and rs12427129 polymorphisms significantly increased the risk of overall cancer. Stratified analysis by cancer type showed that the rs4759314 polymorphism significantly increased the risk of gastric cancer and cervical cancer, and the rs920778 polymorphism notably elevated the risk of gastrointestinal cancer, cervical cancer and gastric cancer. In a meta-analysis study conducted by Xu *et al*. (2019) on 21 published studies, it was found that *HOTAIR* rs920778 and rs12826786 polymorphisms significantly increased the risk of cancer. They did not observe any association between rs4759314, rs1899663, rs874945 and cancer susceptibility.

In another meta-analysis study performed by Ge *et al*. (2017), it was shown that *HOTAIR* rs920778 and rs874945 polymorphisms significantly increased the risk of cancer. Also, they reported a decrease in cancer risk for the rs7958904 variant. No association between rs4759314 and rs1899663 polymorphisms and cancer susceptibility was found in their study.

The present study provides the largest meta-analysis on the association between *HOTAIR* polymorphisms and cancer risk up to 1 May 2019. However, several limitations existed in this study. First, evident heterogeneity was observed in several genetic models, and we were not able to address the exact source of this heterogeneity through stratified analysis and sensitivity analyses. It may be due to differences in ethnicity, source and selection of control, cancer types, age distribution and lifestyle factors. Also, only studies published in English were considered. Moreover, all analyses were primarily based on unadjusted ORs due to unavailability of raw data. Finally, the sample size of most polymorphisms, especially in stratified analysis, was relatively small, which may result in false positives and underpowered results.

Conclusion

Our current meta-analysis findings provided evidence that there is a significant increase in the possibility of cancer development for *HOTAIR* rs4759314, rs920778, rs12826786, rs874945 and rs12427129 polymorphisms. Subgroup analyses by cancer type showed that the rs4759314 polymorphism considerably elevated the risk of gastric cancer and cervical cancer. The rs920778 polymorphism was positively associated with gastrointestinal cancer, cervical cancer and gastric cancer development. We suggest future studies with large-scale samples to further confirm our results.

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