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REVIEW ARTICLE

Association between genetic polymorphisms of long noncoding RNA H19 and cancer risk: a meta-analysis

MOHAMMAD HASHEMI[1,2]*, ABDOLKARIM MOAZENI-ROODI[3], SAHEL SARABANDI[2], SHIMA KARAMI[2] and SAEID GHAVAMI[4,5]

[1] *Genetics of Non-communicable Disease Research Centre, Zahedan University of Medical Sciences, Zahedan 9816743181, Iran*
[2] *Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan 9816743181, Iran*
[3] *Department of Clinical Biochemistry, Iranshahr University of Medical Sciences, Iranshahr 9916643535, Iran*
[4] *Department of Human Anatomy and Cell Science, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB R3E 3P5, Canada*
[5] *Research Institute in Oncology and Hematology, Cancer Care Manitoba, University of Manitoba, Winnipeg R3E 0V9, Canada*
*For correspondence. E-mail: mhd.hashemi@gmail.com; hashemim@zaums.ac.ir.

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Abstract. Long noncoding RNA (lncRNA) H19, a well-known oncogenic lncRNA, is overexpressed in various cancers. Several studies have investigated the association between polymorphisms in lncRNA H19 and the risk of various cancer types; however, the findings were inconsistent. In this study, we performed a meta-analysis to identify the precise association between H19 polymorphisms and cancer risk. Appropriate studies were retrieved from searching Web of Science, PubMed, Scopus, and Google scholar databases, updated 25 November 2018. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of the association between H19 polymorphisms and cancer risk. Our findings revealed that the H19-rs217727 C>T polymorphism is significantly associated with an increased risk of overall cancer in homozygous codominant (OR = 1.28, 95%CI = 1.04–1.57, $P = 0.020$, TT vs CC), dominant (OR = 1.20, 95% CI = 1.04–1.37, $P = 0.010$, CT+TT vs CC), recessive (OR = 1.21, 95% CI = 1.00–1.46, $P = 0.048$, TT vs CT+CC), and allele (OR = 1.16, 95%CI = 1.05–1.28, $P = 0.003$, T vs C) genetic models. No significant correlations were observed between H19: rs2839698 G>A, rs2107425 C>T, rs2735971 C>T, rs3024270 G>C, rs3741219 T>C, rs2839701 C>G, rs2735469 C>T, rs17658052 G>A, and rs3741216 T>A polymorphisms and overall cancer risk. Stratified analysis by cancer type proposed that the rs217727 variant is associated with increased risk of oral squamous cell carcinoma (OSCC) and lung cancer, whereas the rs2839698 variant is associated with increased risk of gastrointestinal cancer. Taken together, these findings support an association between H19 rs217727, and rs2839698 polymorphisms and cancer susceptibility. Larger and well-designed studies are necessary to further confirm these findings in detail.

Keywords. long noncoding RNA H19; polymorphism; cancer; meta-analysis.

Introduction

Cancer is a major burden of disease globally. In 2018 alone, there is about 18.1 million new cases and 9.6 million cancer-related deaths (Bray *et al.* 2018). However, the aetiology of cancer is still unclear. Accumulated evidence indicates that multifaceted processes involving genetic loci and environmental factors play an important role in the development of cancer (Lichtenstein *et al.* 2000). Single-nucleotide polymorphisms (SNPs) are the most common type of genetic variation among people and contribute to cancer development (Hashemi *et al.* 2018; Moazeni-Roodi and Hashemi 2018).

Noncoding RNAs (ncRNAs) are classified into short ncRNAs and long ncRNAs (lncRNAs). LncRNAs consist of a single-strand, longer than 200 nucleotides and cannot be translated into protein, although some produce small functional peptides (de Oliveira *et al.* 2018).

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

First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	Cases					Controls					HWE (p)
rs217727								CC	CT	TT	C	T	CC	CT	TT	C	T	
Abdollahzadeh S	2018	Iran	Asian	Breast cancer	PB	PCR-RFLP	150/100	116	29	5	261	39	86	14	0	186	14	0.451
Cui P	2018	China	Asian	Breast cancer	PB	Real-time	1488/1675	611	692	185	1914	1062	685	773	217	2143	1207	0.963
Guo QY	2017	China	Asian	OSCC	PB	Illumina	362/740	101	181	80	383	341	255	348	137	858	622	0.342
Hassanzarei S	2017	Iran	Asian	Breast cancer	PB	PCR-RFLP	230/240	71	132	27	274	186	125	113	2	363	117	<0.001
He TD	2017	China	Asian	Osteosarcoma	PB	TaqMan	193/383	79	102	12	260	126	195	165	23	555	211	0.121
Hu PH	2017	China	Asian	Pancreatic cancer	PB	TaqMan	416/416	133	200	83	466	366	128	196	92	452	380	0.302
Hua Q	2016	China	Asian	Bladder cancer	HB	TaqMan	1046/1394	431	467	148	1329	763	573	665	156	1811	977	0.074
Jin T	2016	China	Asian	Cervical cancer	PB	MassARRAY	246/284	117	103	26	337	155	169	99	16	437	131	0.765
Li L	2018	China	Asian	Lung cancer	HB	TaqMan	555/618	210	250	95	670	440	246	305	67	797	439	0.054
Li S	2016	China	Asian	Colorectal cancer	PB	TaqMan	1147/1203	480	514	153	1474	820	456	570	177	1482	924	0.959
Li Z	2018	China	Asian	Bladder cancer	HB	TaqMan	200/200	51	140	9	242	158	84	90	26	258	142	0.806
Verhaegh GW	2008	Netherlands	Caucasian	Bladder Cancer	PB	PCR-RFLP	177/204	114	59	4	287	67	115	80	9	310	98	0.288
Xia Z	2016	China	Asian	Breast Cancer	PB	PCR-RFLP	464/467	160	156	148	476	452	139	212	116	490	444	0.052
Yang C	2015	China	Asian	Gastric cancer	PB	TaqMan-MGB	500/500	160	252	88	572	428	193	244	63	630	370	0.296
Yin Z	2018	China	Asian	Lung Cancer	HB	Illumina	556/395	204	264	88	672	440	165	172	58	502	288	0.232
Yuan Z	2018	China	Asian	OSCC	PB	MassARRAY	431/984	186	194	51	566	296	488	423	73	1399	569	0.151
rs2839698								GG	GA	AA	G	A	GG	GA	AA	G	A	
Gong WJ	2016	China	Asian	Lung cancer	HB	MassARRAY	496/206	237	220	39	694	298	99	80	27	278	134	0.098
Guo QY	2017	China	Asian	OSCC	PB	Illumina	362/741	133	171	58	437	287	244	377	120	865	617	0.202
Hassanzarei S	2017	Iran	Asian	Breast cancer	PB	PCR-RFLP	230/240	166	64	0	396	64	222	18	0	462	18	0.546
He TD	2017	China	Asian	Osteosarcoma	PB	TaqMan	193/383	83	98	12	264	122	178	175	30	531	235	0.146
Hua Q	2016	China	Asian	Bladder cancer	HB	TaqMan	1049/1397	552	418	79	1522	576	729	565	103	2023	771	0.651
Li S	2016	China	Asian	Colorectal cancer	PB	TaqMan	1147/1203	583	462	102	1628	666	666	462	75	1794	612	0.666
Verhaegh GW	2008	Netherlands	Caucasian	Bladder Cancer	PB	PCR-RFLP	177/204	54	74	49	182	172	52	109	43	213	195	0.313
Yang C	2015	China	Asian	Gastric cancer	PB	TaqMan-MGB	500/500	250	195	55	695	305	284	178	38	746	254	0.175
Yang ML	2018	China	Asian	HCC	HB	KASP	466/462	215	211	40	641	291	245	185	32	675	249	0.714
rs2107425								CC	CT	TT	C	T	CC	CT	TT	C	T	
Barnholtz-Sloan JS	2010	USA	Mixed	Breast cancer	PB	Illumina	1962/1776	765	906	291	2436	1488	691	817	268	2199	1353	0.299
Butt S	2012	Sweden	Caucasian	Breast cancer	PB	MassArray	679/1355	361	250	68	972	386	637	573	145	1847	863	0.342
Bhatti P	2008	USA	Caucasian	Breast cancer	PB	MassARRAY	824/1073	392	432		–	–	502	571		–	–	–
Gong WJ	2016	China	Asian	Lung cancer	HB	MassARRAY	479/203	181	235	63	597	361	79	96	28	254	152	0.892
Quaye L	2009	Mixed	Caucasian	Ovarian cancer	PB	TaqMan	1460/2463	767	544	149	2078	842	1118	1098	247	3334	1592	0.345
Song H	2009	Mixed	Caucasian	Ovarian cancer	PB	TaqMan	5366/8538	2619	2192	555	7430	3302	4029	3667	842	11725	5351	0.857
Verhaegh GW	2008	Netherlands	Caucasian	Bladder Cancer	PB	PCR-RFLP	177/204	92	65	20	249	105	89	96	19	274	134	0.340
Yin Z	2018	China	Asian	Lung Cancer	HB	Illumina	556/395	161	266	129	588	524	140	185	70	465	325	0.513
rs2735971								CC	CT	TT	C	T	CC	CT	TT	C	T	
Guo QY	2017	China	Asian	OSCC	PB	Illumina	461/739	191	141	129	523	399	351	308	80	1010	468	0.315
He TD	2017	China	Asian	Osteosarcoma	PB	TaqMan	193/383	88	94	11	270	116	169	182	32	520	246	0.079

Table 1. (*contd*)

First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping Method	Case/ control	Cases					Controls					HWE (p)
rs217727								CC	CT	TT	C	T	CC	CT	TT	C	T	
Hua Q	2016	China	Asian	Bladder cancer	HB	TaqMan	1049/1396	704	302	43	1710	388	928	422	46	2278	514	0.815
Li S	2016	China	Asian	Colorectal cancer	PB	TaqMan	1147/1203	773	334	40	1880	414	765	398	40	1928	478	0.175
Li Z	2018	China	Asian	Bladder cancer	HB	TaqMan	200/200	128	62	10	318	82	126	70	4	322	78	0.104
Yang ML	2018	China	Asian	HCC	HB	KASP	465/465	327	126	12	780	150	313	139	13	765	165	0.603
rs3024270								GG	GC	CC	G	C	GG	GC	CC	G	C	
Guo QY	2017	China	Asian	OSCC	PB	Illumina	362/740	104	183	75	391	333	245	350	145	840	640	0.321
He TD	2017	China	Asian	Osteosarcoma	PB	TaqMan	193/383	85	91	17	261	125	173	179	31	525	241	0.101
Hua PH	2016	China	Asian	Bladder cancer	HB	TaqMan	1047/1395	346	527	174	1219	875	447	688	260	1582	1208	0.869
Li S	2016	China	Asian	Colorectal cancer	PB	TaqMan	1147/1203	385	527	235	1297	997	420	582	201	1422	984	0.979
Li Z	2018	China	Asian	Bladder cancer	HB	TaqMan-MGB	200/200	83	101	16	267	133	81	97	22	259	141	0.377
Yang ML	2018	China	Asian	HCC	HB	KASP	471/466	151	225	95	527	415	170	215	81	555	377	0.361
rs3741219								TT	TC	CC	T	C	TT	TC	CC	T	C	
Abdollahzadeh S	2018	Iran	Asian	Breast cancer	PB	PCR-RFLP	150/100	119	24	7	262	38	80	17	3	177	23	0.099
Cui P	2018	China	Asian	Breast cancer	PB	Real-time	1491/1677	782	582	127	2146	836	832	706	139	2370	984	0.529
Hassanzarei S	2017	Iran	Asian	Breast cancer	PB	PCR-RFLP	230/240	63	126	41	252	208	109	102	29	320	160	0.498
Xia Z	2016	China	Asian	Breast Cancer	PB	PCR-RFLP	464/467	238	186	40	662	266	245	182	40	672	262	0.456
Yang C	2015	China	Asian	Gastric cancer	PB	TaqMan-MGB	500/500	260	187	53	707	293	268	189	43	725	275	0.245
rs2839701								CC	CG	GG	C	G	CC	CG	GG	C	G	
Cui P	2018	China	Asian	Breast cancer	PB	Real-time	1490/1677	762	600	128	2124	856	801	732	144	2334	1020	0.200
Jiang Y	2012	China	Asian	Breast cancer	PB	TaqMan	858/887	404	370	84	1178	538	449	354	84	1252	522	0.244
Yuan Z	2018	China	Asian	OSCC	PB	MassARRAY	444/984	205	188	51	598	290	507	402	75	1416	552	0.703
rs2735469								CC	CT	TT	C	T	CC	CT	TT	C	T	
Verhaegh GW	2008	Netherlands	Caucasian	Bladder Cancer	PB	PCR-RFLP	177/204	119	51	7	289	65	136	64	4	336	72	0.257
Yin Z	2018	China	Asian	Lung Cancer	HB	Illumina	556/395	507	46	3	1060	52	359	36	0	754	36	0.343
rs17658052								GG	GA	AA	G	A	GG	GA	AA	G	A	
Verhaegh GW	2008	Netherlands	Caucasian	Bladder Cancer	PB	PCR-RFLP	177/204	151	26	0	328	26	181	23	0	385	23	0.394
Yin Z	2018	China	Asian	Lung Cancer	HB	Illumina	556/395	507	47	2	1061	51	371	24	0	766	24	0.533
rs3741216								TT	TA	AA	T	A	TT	TA	AA	T	A	
Hassanzarei S	2017	Iran	Asian	Breast cancer	PB	PCR-RFLP	230/240	204	26	0	434	26	175	65	0	415	65	0.015
Yang C	2015	China	Asian	Gastric cancer	PB	TaqMan-MGB	500/500	380	102	18	862	138	379	109	12	867	133	0.221

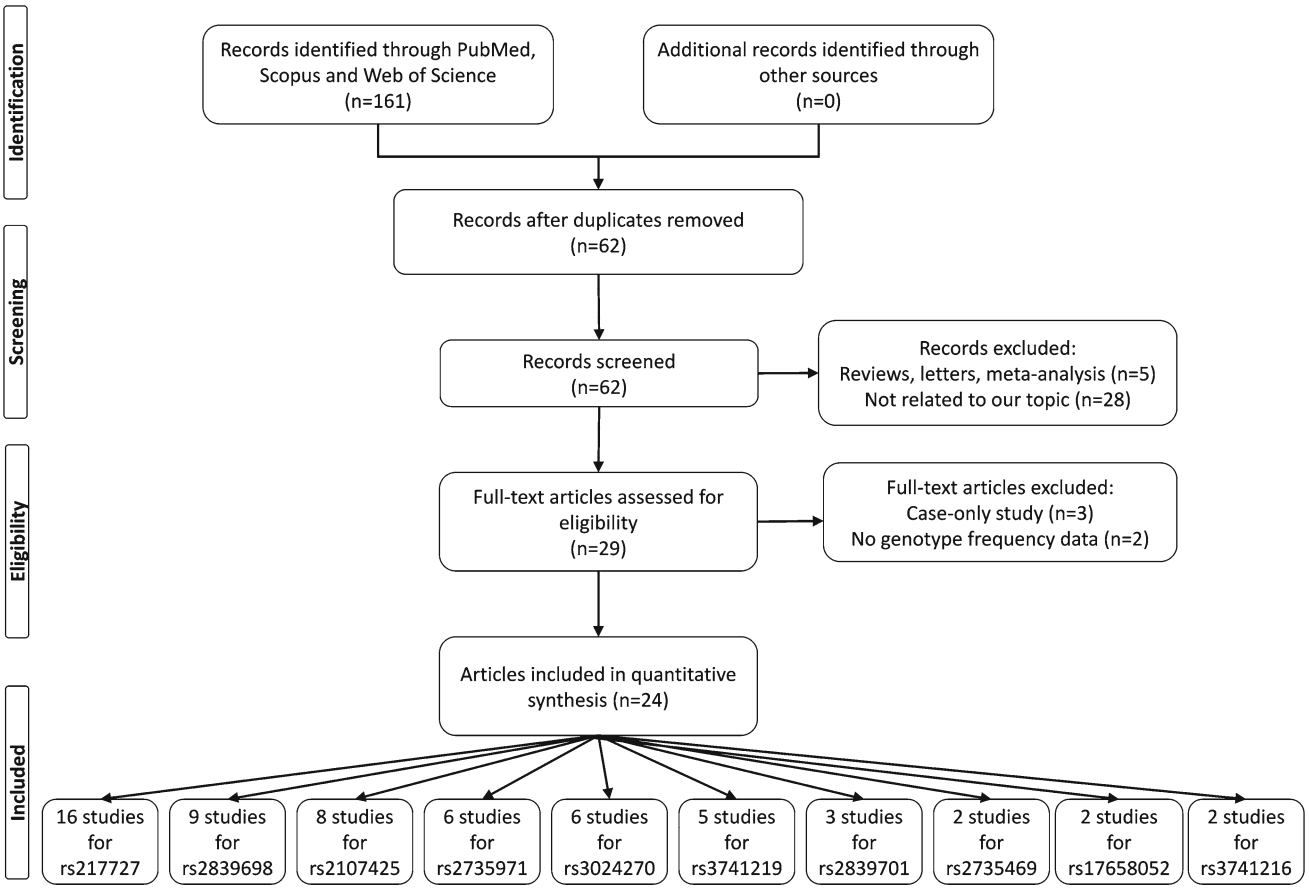

Figure 1. Flowchart of the study selection procedure.

These transcripts may have critical roles in a wide range of biological processes by regulation of gene expression at various levels, including chromatin remodelling, transcription, and post-transcription (Hashemi *et al.* 2016; Xue *et al.* 2017). LncRNAs are involved in cell cycle regulation and affect proliferation, differentiation, apoptosis, as well as being involved in the pathogenesis of cancer (Fatica and Bozzoni 2014; Iyer *et al.* 2015; Do and Kim 2018).

The lncRNA H19 is located on the short arm of chromosome 11 (11p15.5) and is 2.3-kb long (Gabory *et al.* 2010). It functions as an oncogenic molecule in various cancer cells (Matouk *et al.* 2007; Xia *et al.* 2014; Wang *et al.* 2015; Li *et al.* 2017b). Polymorphisms of H19 have been described to be involved in cancer susceptibility. Several studies examined the association between H19 polymorphisms and the risk of various cancers in different populations, but the the findings were inconclusive and inconsistent (Bhatti *et al.* 2008; Verhaegh *et al.* 2008; Quaye *et al.* 2009; Song *et al.* 2009; Barnholtz-Sloan *et al.* 2010; Butt *et al.* 2012; Jiang *et al.* 2012; Yang *et al.* 2015; Gong *et al.* 2016; Hua *et al.* 2016; Jin *et al.* 2016; Li *et al.* 2016; Xia *et al.* 2016; Guo *et al.* 2017; Hassanzarei *et al.* 2017; He *et al.* 2017; Hu *et al.* 2017; Abdollahzadeh and Ghorbian 2018; Cui *et al.* 2018; Li *et al.* 2018; Li and Niu 2018; Yang *et al.* 2018; Yin *et al.* 2018; Yuan *et al.* 2018). In the present study, we conducted an updated meta-analysis and aimed to identify an accurate association between H19 polymorphisms and cancer susceptibility.

Methods

Literature search

We performed a comprehensive search for relevant studies focussing on H19 polymorphisms in Web of Science, PubMed, Scopus and Google Scholar databases, updated 25 November 2018. The search keywords were 'cancer or carcinoma or tumor or neoplasms' and 'H19' and 'polymorphism or mutation or variant'. The meta-analysis comprised relevant studies that met the following inclusion criteria: (i) original case–control studies; (ii) studies contain sufficient genotyping data of H19 polymorphisms in both patients and control subjects. The exclusion criteria were: (i) case reports, conference abstract, meta-analysis, and duplication data; (ii) insufficient genotyping information provided. This article does not contain any studies with human participants or animals performed by any of the authors.

Table 2. The pooled ORs and 95% CIs for the association between H19 polymorphisms and cancer susceptibility.

			Association test			Heterogeneity			Publication bias tests	
Polymorphism	Number	Genetic model	OR (95% CI)	Z	*P*	χ^2	I^2 (%)	*P*	Egger's test *P* value	Begg's test *P* value
rs217727	16	CT vs CC	1.15 (1.00–1.33)	1.92	0.054	63.53	76.4	0.000	0.037	0.038
		TT vs CC	1.28 (1.04–1.57)	2.33	0.020	54.69	72.6	0.000	0.165	0.125
		CT+TT vs CC	1.20 (1.04–1.37)	2.56	0.010	66.20	77.3	0.000	0.017	0.038
		TT vs CT+CC	1.21 (1.00–1.46)	1.98	0.048	53.80	72.1	0.000	0.507	0.400
		T vs C	1.16 (1.05–1.28)	2.96	0.003	64.15	76.6	0.000	0.029	0.150
rs2839698	9	AG vs GG	1.18 (0.96–1.44)	1.53	0.126	39.28	79.6	0.000	0.338	0.677
		AA vs GG	1.11 (0.88–1.40)	0.92	0.360	15.10	53.6	0.035	0.472	0.458
		AG+AA vs GG	1.19 (0.97–1.44)	1.69	0.091	39.29	79.6	0.000	0.353	0.677
		AA vs AG+GG	1.11 (0.90–1.38)	0.99	0.323	14.48	51.6	0.043	0.435	0.138
		A vs G	1.15 (0.99–1.33)	1.80	0.072	38.04	79.0	0.000	0.238	0.404
rs2107425	8	CT vs CC	0.89 (0.78–1.01)	1.74	0.082	22.54	73.4	0.001	0.922	0.881
		TT vs CC	1.00 (0.92–1.08)	0.09	0.927	9.03	33.6	0.172	0.816	0.881
		CT+TT vs CC	0.92 (0.82–1.03)	1.50	0.134	23.77	70.6	0.001	0.942	1.00
		TT vs CT+CC	1.04 (0.96–1.13)	1.04	0.298	4.72	0.0	0.581	0.717	0.652
		T vs C	0.96 (0.88–1.04)	0.95	0.341	19.18	68.7	0.004	0.972	0.652
rs2735971	6	CT vs CC	0.88 (0.80–0.97)	2.47	0.140	1.55	0.00	0.908	0.813	0.348
		TT vs CC	1.31 (0.77–2.23)	1.01	0.315	27.45	81.8	0.000	0.326	0.573
		CT+TT vs CC	0.96 (0.87–1.05)	0.90	0.371	8.40	40.5	0.136	0.763	0.851
		TT vs CT+CC	1.37 (0.78–2.39)	1.10	0.273	32.17	84.5	0.000	0.272	0.851
		T vs C	1.04 (0.84–1.30)	0.40	0.692	35.07	85.7	0.000	0.897	0.573
rs3024270	6	CG vs GG	1.04 (0.94–1.15)	0.82	0.415	2.63	0.0	0.757	0.278	0.573
		CC vs GG	1.09 (0.96–1.25)	1.32	0.187	8.18	38.9	0.147	0.868	0.348
		CG+CC vs GG	1.06 (0.96–1.16)	1.13	0.257	3.77	0.0	0.583	0.522	0.851
		CC vs CG+GG	1.07 (0.95–1.20)	1.05	0.291	8.59	41.8	0.127	0.715	0.573
		C vs G	1.05 (0.98–1.12)	1.34	0.179	6.91	27.7	0.227	0.906	0.573
rs3741219	5	CT vs TT	1.12 (0.85–1.46)	0.79	0.428	16.71	76.1	0.002	0.256	0.327
		CC vs TT	1.27 (0.91–1.76)	1.42	0.156	9.00	55.6	0.061	0.276	0.321
		CT+CC vs TT	1.15 (0.88–1.51)	1.02	0.307	19.04	79.0	0.001	0.217	0.624
		CC vs CT+TT	1.13 (0.95–1.36)	1.35	0.176	2.87	0.0	0.580	0.248	0.327
rs2839701	3	CG vs CC	1.04 (0.84–1.30)	0.33	0.744	7.59	73.7	0.022	0.245	0.602
		GG vs CC	1.17 (0.85-1.62)	0.96	0.335	6.05	66.9	0.049	0.187	0.117
		CG+GG vs CC	1.06 (0.85–1.33)	0.53	0.593	9.21	78.3	0.010	0.138	0.117
		GG vs CG+CC	1.15 (0.89–1.48)	1.03	0.303	4.16	51.9	0.125	0.345	0.117
		G vs C	1.07 (0.90–1.27)	0.75	0.456	9.38	78.7	0.009	0.002	0.117
		C vs T	1.12 (0.93–1.35)	1.18	0.238	15.48	74.2	0.004	0.242	0.327
rs2735469	2	CT vs CC	0.91 (0.66–1.25)	0.60	0.551	0.00	0.0	0.984	–	–
		TT vs CC	2.29 (0.72–7.28)	1.41	0.158	0.31	0.0	0.576	–	–
		CT+TT vs CC	0.97 (0.71–1.32)	0.20	0.845	0.00	0.0	0.971	–	–
		TT vs CT+CC	2.35 (0.75–7.41)	1.46	0.144	0.30	0.0	0.584	–	–
		T vs C	1.04 (0.76–1.38)	0.27	0.784	0.01	0.0	0.942	–	–
rs17658052	2	GA vs GG	1.40 (0.95–2.07)	1.70	0.090	0.02	0.0	0.879	–	–
		AG+AA vs GG	1.43 (0.97–2.11)	1.83	0.068	0.06	0.0	0.808	–	–
		A vs G	1.44 (0.99–2.10)	1.91	0.056	0.14	0.0	0.709	–	–
rs3741216	2	AT vs TT	0.58 (0.22–1.54)	1.10	0.272	11.30	91.2	0.001	–	–
		AT+AA vs TT	0.59 (0.211–1.68)	0.98	0.326	13.00	92.3	0.000	–	–
		A vs T	0.64 (0.24–1.72)	0.87	0.382	13.35	92.5	0.000	–	–

Data extraction

Two investigators independently searched the literature and extracted the relevant data from appropriate studies. The following information was documented for each study: first author, publication date, country, ethnicity of participants, source of control, cancer type, genotyping methods of H19 polymorphisms, genotype distributions in cases and controls, and results of the Hardy–Weinberg equilibrium (HWE) test (table 1).

Statistical analysis

All the analyses were carried out using STATA 14.1 (Stata Corporation, College Station, USA). Departure from HWE in controls was examined by the chi-square test. The strength of the association between H19 polymorphisms and cancer risk was assessed by pooled odds ratios (ORs) and their 95% confidence intervals (CIs). The Z-test was used to assess statistical significance of the pooled OR. We estimated the interstudy heterogeneity by the Q-test and I^2

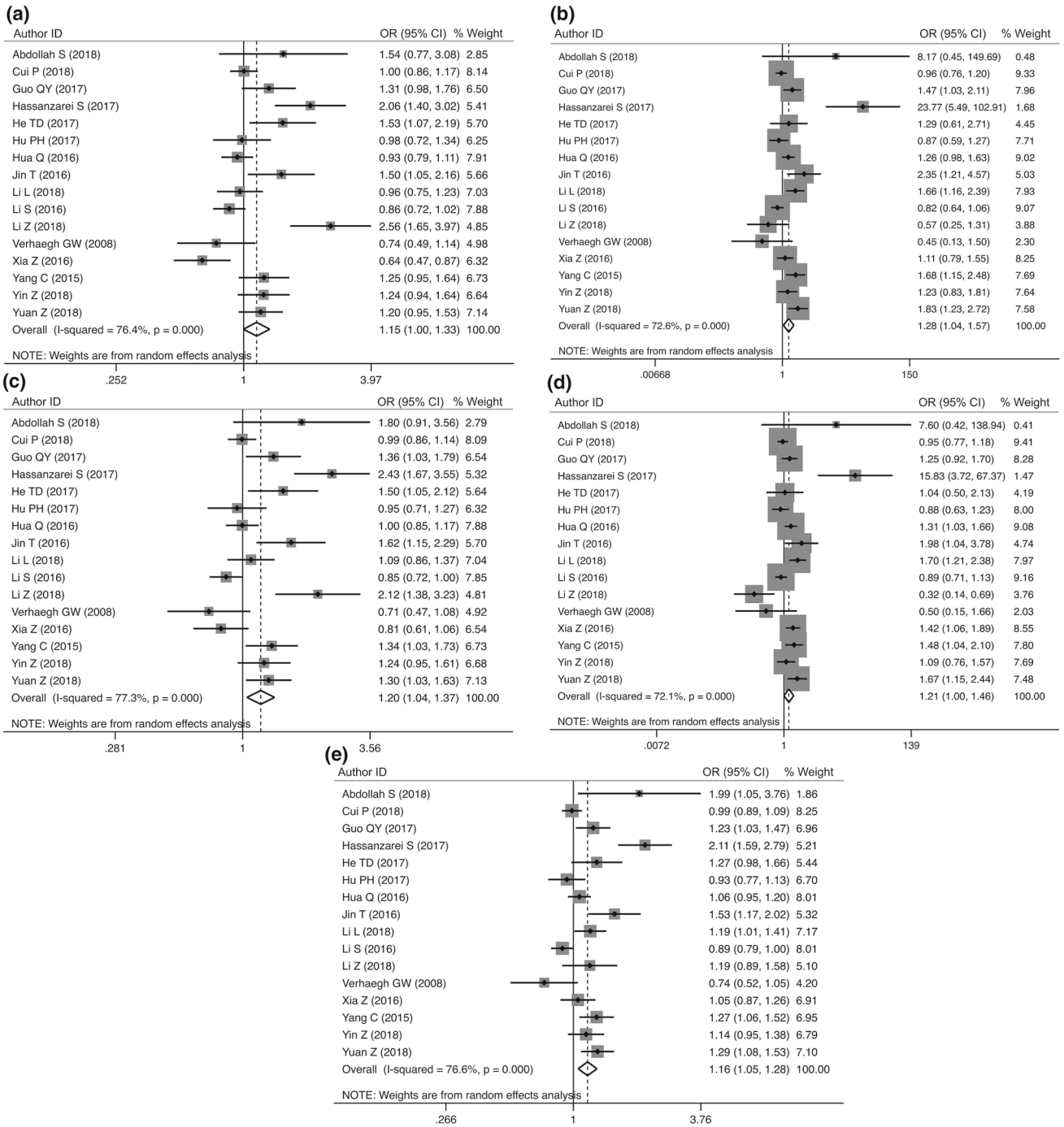

Figure 2. Forest plot representing the association between the H19 rs217727 polymorphism and cancer risk under (a) heterozygous codominant (CT vs CC), (b) homozygous codominant (TT vs CC), (c) dominant (CT+TT vs CC), (d) recessive (TT vs CT+CC), and (e) allele genetic models (T vs C).

test, with a *P* value less than 0.10 indicating the presence of heterogeneity. If heterogeneity existed then a random-effect model was employed else a fixed-effect model was used. Stratified analyses by tumour type was also applied for each genetic comparison model. We assessed publication bias using funnel plots for visual inspection and by conducting quantitative estimations with the Egger's test. Sensitivity analysis was performed by sequentially ignoring one single study at a time to determine the impact of individual datasets on the pooled ORs.

Results

Study characteristics

A flowchart of the study selection procedure is shown in figure 1. Primarily, 59 case–control studies from 24

publications (Bhatti *et al.* 2008; Verhaegh *et al.* 2008; Song *et al.* 2009; Quaye *et al.* 2009; Barnholtz-Sloan *et al.* 2010; Butt *et al.* 2012; Jiang *et al.* 2012; Yang *et al.* 2015; Jin *et al.* 2016; Gong *et al.* 2016; Hua *et al.* 2016; Li *et al.* 2016; Xia *et al.* 2016; Guo *et al.* 2017; Hassanzarei *et al.* 2017; He *et al.* 2017; Hu *et al.* 2017; Li *et al.* 2018; Li and Niu 2019; Abdollahzadeh and Ghorbian 2018; Cui *et al.* 2018; Yang *et al.* 2018; Yin *et al.* 2018; Yuan *et al.* 2018) that met our inclusion criteria were identified. A total of 16 studies on rs217727 (8161 cases and 9803 controls), nine studies on rs2839698 (4620 cases and 5336 controls), eight studies on rs2107425 (6165 cases and 8722 controls), six studies on rs2735971 (3515 cases and 4386 controls), six studies on rs3024270 (3420 cases and 4387 controls), five studies on rs3741219 (2835 cases and 2984 controls), three studies on rs2839701 (2792 cases and 3548 controls), two studies on rs2735469 (733 cases and 599 controls), two studies on rs17658052 (733 cases and 599 controls), and two studies on rs3741216 (730 cases and 740 controls) were included in the meta-analysis. The main characteristics of these studies are provided in table 1.

Main analysis results

The main results of our meta-analysis and the heterogeneity tests are depicted in table 2. The findings revealed that the rs217727 C>T polymorphism is significantly associated with an increased risk of overall cancer in homozygous codominant (OR = 1.28, 95% CI = 1.04–1.57, $P = 0.020$, TT vs CC), dominant (OR = 1.20, 95% CI = 1.04–1.37, $P = 0.010$, CT+TT vs CC), recessive (OR = 1.21, 95% CI = 1.00–1.46, $P = 0.048$, TT vs CT +CC), and allele (OR = 1.16, 95% CI = 1.05–1.28, $P = 0.003$, T vs C) genetic models (figure 2; table 2). Overall, no significant association was observed between H19 rs3741219 T>C, rs2839701 C>G, rs2839698 G>A, rs2107425 C>T, rs2735971 C>T, rs3024270 G>C, rs2735469 C>T, rs17658052 G>A, and rs3741216 T>A polymorphisms and cancer risk in any of the genetic models tested (table 2).

Subgroup analysis results

Stratified analysis of H19-rs217727, H19-rs2839698 and H19-rs2107425 polymorphisms by cancer type was performed (table 3). The data showed that the rs217727 variant was associated with increased risk of oral squamous cell carcinoma (OSCC) ($n = 2$ studies) and lung cancer ($n = 2$ studies). In addition, the findings indicated an association between the rs2839698 variant and increased risk of gastrointestinal cancer ($n = 3$ studies). The rs2107425 variant was not associated with any type of cancer.

Table 3. Stratified analysis of H19 rs217727 and rs2107425 polymorphisms on cancer susceptibility.

rs217727	No.	CT vs CC	*P*	TT vs CC	*P*	CT+TT vs CC	*P*	TT vs CT+CC	*P*	T vs C	*P*
Gastrointestinal cancer	6	1.08 (0.84–1.38)	0.56	0.99 (0.73–1.34)	0.94	1.06 (0.85–1.32)	0.61	0.94 (0.69–1.28)	0.68	1.01 (0.89–1.16)	0.86
Breast cancer	4	1.15 (0.73–1.80)	0.55	1.91 (0.90–4.01)	0.09	1.31 (0.84–2.04)	0.24	1.82 (0.94–3.51)	0.07	1.36 (0.96–1.91)	0.08
Bladder cancer	3	1.20 (0.64–2.23)	0.57	0.80 (0.40–1.61)	0.54	1.13 (0.68–1.88)	0.63	0.63 (0.22–1.80)	0.39	1.01 (0.82–1.25)	0.92
OSCC	2	1.25 (1.04–1.50)	0.02	1.63 (1.25–2.12)	0.0003	1.32 (1.11–1.57)	0.002	1.42 (1.07–1.88)	0.02	1.26 (1.11–1.42)	0.0003
Lung cancer	2	1.08 (0.84–1.39)	0.54	1.44 (1.07–1.94)	0.02	1.15 (0.97–1.37)	0.12	1.37 (0.89–2.11)	0.15	1.17 (1.03–1.33)	0.01
rs2839698		AG vs GG	*P*	AA vs GG	*P*	AG+AA vs GG	*P*	AA vs AG+GG	*P*	A vs G	*P*
Gastrointestinal cancer	3	1.20 (1.06–1.36)	0.005	1.55 (1.23–1.95)	0.0002	1.43 (1.14–1.79)	0.002	1.20 (1.06–1.36)	0.005	1.23 (1.12–1.35)	< 0.0001
Bladder cancer	2	0.85 (0.59–1.24)	0.40	1.03 (0.79–1.36)	0.82	1.02 (0.75–1.39)	0.88	0.85 (0.5–1.24)	0.40	1.00 (0.89–1.12)	0.99
rs2107425		CT vs CC	*P*	TT vs CC	*P*	CT+TT vs CC	*P*	TT vs CT+CC	*P*	T vs C	*P*
Breast cancer	3	0.89 (0.69–1.15)	0.36	0.94 (0.97–1.10)	0.43	0.92 (0.79–1.06)	0.25	0.97 (0.83–1.13)	0.77	0.93 (0.80–1.08)	0.33
Ovarian cancer	2	0.82 (0.65–1.04)	0.10	0.98 (0.86–1.10)	0.70	0.84 (0.86–1.05)	0.13	1.05 (0.95–1.16)	0.37	0.92 (0.80–1.05)	0.20
Lung cancer	2	1.17 (0.94–1.47)	0.17	1.30 (0.81–2.09)	0.28	1.21 (0.95–1.54)	0.12	1.20 (0.82–1.75)	0.34	1.15 (0.92–1.44)	0.23

Heterogeneity and publication bias

Interstudy heterogeneity across studies in pooled analysis is provided in table 2. We found heterogeneity in overall comparisons between studies for rs217727 and rs2839698. For rs2107425, heterogeneity was observed in heterozygous codominant, and recessive genetic models.

Begg's funnel plot and Egger's test were implemented to estimate the publication bias of the included literature (table 2; figure 3). The Egger's tests showed no publication bias in homozygous codominant and recessive genetic

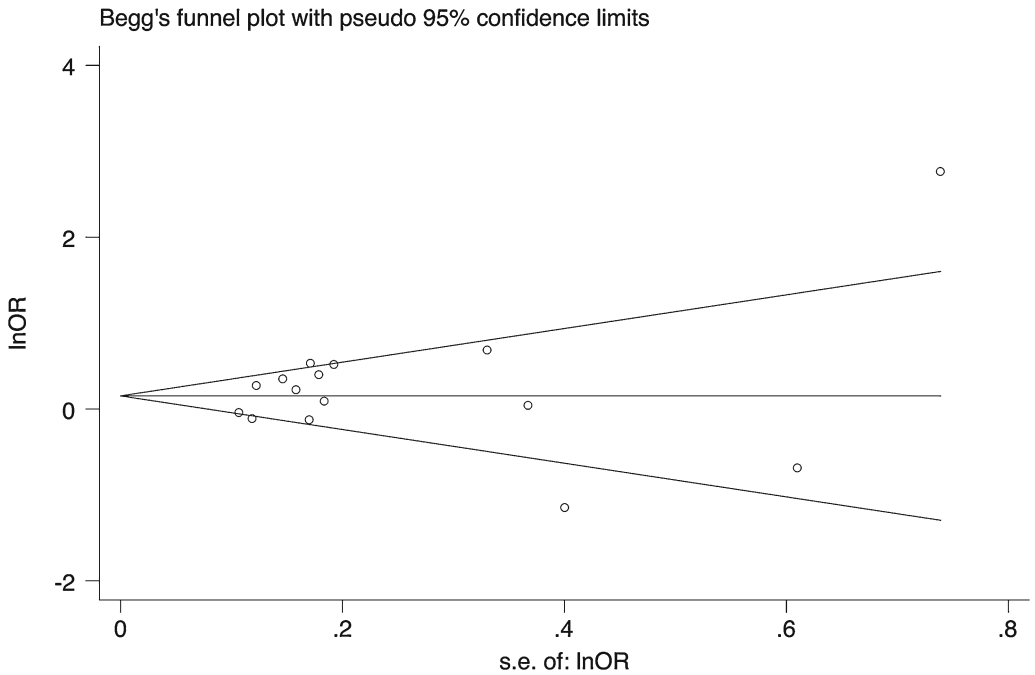

Figure 3. Begg's funnel plot testing publication bias for the association between the H19 rs217727 polymorphism and cancer risk (TT vs CT+CC).

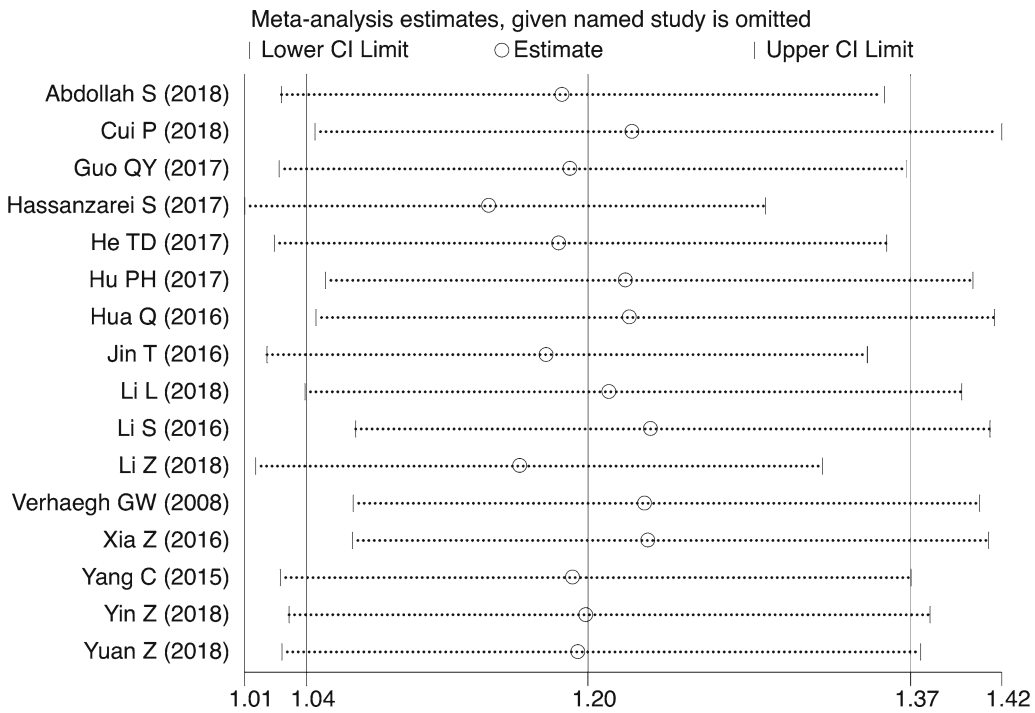

Figure 4. Sensitivity analyses for studies on the association of H19 rs217727 polymorphism and cancer risk (CT+TT vs CC).

models for rs217727 (table 2). In addition, the findings revealed no publication bias for rs2839698, rs2107425, rs2735971, rs3024270, rs3741219 and rs2839701 polymorphisms (table 2).

Sensitivity analysis

Sensitivity analysis was carried out to estimate the effects of individual studies on the stability of the results in our meta-analysis. With sequential removal of individual study results from the analysis for rs217727, the pooled ORs remained significantly consistent (figure 4). Therefore, the final pooled results were both stable and reliable.

Discussion

LncRNAs are involved in controlling the expression of other ncRNA, such as microRNAs, or targeting proteins through epigenetic, transcriptional, or post-transcriptional regulation. Genetic variations in lncRNA genes could affect gene expression and may lead to cancer development (Cheetham *et al.* 2013; Zhou *et al.* 2015). Dysregulation of oncogenic lncRNA H19 has been reported in various types of cancer, including breast (Li *et al.* 2017b), gastric (Xia *et al.* 2014), hepatocellular (Matouk *et al.* 2007; Abbastabar *et al.* 2018), and bladder cancer (Matouk *et al.* 2007), choriocarcinoma (Yu *et al.* 2013), and gastrointestinal stromal tumours (Gyvyte *et al.* 2018). Several studies investigated the association between H19 polymorphisms and the risk of various cancers, but rendered inconclusive and inconsistent results. In the present study, we performed an up to date meta-analysis of all available data regarding the association between H19 polymorphisms and the risk of cancer.

Our findings reveled that the rs217727 polymorphism ($n = 16$), but not the rs2839698 ($n = 9$), rs2107425 ($n = 8$), rs2735971 ($n = 6$), rs3024270 ($n = 6$), rs3741219 ($n = 5$), rs2839701 ($n = 3$), rs2735469 ($n = 2$), rs17658052 ($n = 2$), or rs3741216 ($n = 2$) polymorphisms is associated with overall cancer risk.

Stratified analysis by cancer type proposed that the rs217727 variant is associated with increased risk of OSCC ($n = 2$) and lung cancer ($n = 2$), and that prevalence of the rs2839698 polymorphism is positively associated with the risk of gastrointestinal cancer ($n = 3$).

In contrast to our findings, a meta-analysis performed by Lv *et al.* (2017) revealed that lncRNA H19 rs2735971 ($n = 2$), rs2839698 ($n = 4$), and rs3024270 ($n = 2$) polymorphisms, but not rs217727 ($n = 5$), were correlated with overall cancer risk. Another meta-analysis (Li *et al.* 2017a) showed that H19 rs2839698 ($n = 5$), rs2107425 ($n = 8$) and rs217727 ($n = 5$) polymorphisms were not associated with overall cancer risk. Compared with the previous meta-analyses (Li *et al.* 2017a; Lv *et al.* 2017), our analysis includes more relevant research articles (24 published studies), and also the number of studies on each polymorphism was higher. Moreover, more (10) polymorphisms were evaluated, providing a more complete overview of the association between the prevalence of H19 polymorphisms and cancer risk.

Some limitations of our meta-analysis should be taken into consideration. First, heterogeneity was observed among some studies, which may be due to the source of control, cancer type, and difference of ethnicity. Second, in this study, the majority of subjects are of Asian descent, limiting the statistical power for analysis of other ethnicities. Finally, the number of included studies and sample sizes for some of the H19 polymorphisms were relatively low. Accordingly, the results should be interpreted with caution.

In conclusion, the findings of this meta-analysis proposed an association between H19 rs217727 and rs2839698 polymorphisms and cancer susceptibility. Larger and well-designed studies are required to further confirm the exact role of these specific H19 polymorphisms in cancer development, progression, and severity. Ultimately, such polymorphisms could serve as a marker for and potentially therapeutic target in a variety of cancer subtypes.

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References

Abbastabar M., Sarfi M., Golestani A. and Khalili E. 2018 lncRNA involvement in hepatocellular carcinoma metastasis and prognosis. *EXCLI J*. **17**, 900–913.

Abdollahzadeh S. and Ghorbian S. 2018 Association of the study between LncRNA-H19 gene polymorphisms with the risk of breast cancer. *J. Clin. Lab. Anal*. **33**, e22826.

Barnholtz-Sloan J. S., Shetty P. B., Guan X., Nyante S. J., Luo J., Brennan D. J. *et al.* 2010 FGFR2 and other loci identified in genome-wide association studies are associated with breast cancer in African–American and younger women. *Carcinogenesis* **31**, 1417–1423.

Bhatti P., Doody M. M., Alexander B. H., Yuenger J., Simon S. L., Weinstock R. M. *et al.* 2008 Breast cancer risk polymorphisms and interaction with ionizing radiation among US radiologic technologists. *Cancer Epidemiol. Biomark. Prev*. **17**, 2007–2011.

Bray F., Ferlay J., Soerjomataram I., Siegel R. L., Torre L. A., Jemal A. 2018 Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin*. **68**, 394–424.

Butt S., Harlid S., Borgquist S., Ivarsson M., Landberg G., Dillner J. *et al.* 2012 Genetic predisposition, parity, age at first childbirth and risk for breast cancer. *BMC Res. Notes* **5**, 414.

Cheetham S. W., Gruhl F., Mattick J. S. and Dinger M. E. 2013 Long noncoding RNAs and the genetics of cancer. *Br. J. Cancer* **108**, 2419–2425.

Cui P., Zhao Y., Chu X., He N., Zheng H., Han J. *et al.* 2018 SNP rs2071095 in LincRNA H19 is associated with breast cancer risk. *Breast Cancer Res. Treat*. **171**, 161–171.

de Oliveira J. C., Oliveira L. C., Mathias C., Pedroso G. A., Lemos D. S., Salviano-Silva A. *et al.* 2018 LncRNAs in cancer: another layer of complexity. *J. Gene Med*. **21**, e3065.

Do H. and Kim W. 2018 Roles of oncogenic long non-coding RNAs in cancer development. *Genomics Inform*. **16**, e18.

Fatica A. and Bozzoni I. 2014 Long non-coding RNAs: new players in cell differentiation and development. *Nat. Rev. Genet*. **15**, 7–21.

Gabory A., Jammes H. and Dandolo L. 2010 The H19 locus: role of an imprinted noncoding RNA in growth and development. *BioEssays* **32**, 473–480.

Gong W. J., Yin J. Y., Li X. P., Fang C., Xiao D., Zhang W. *et al.* 2016 Association of well-characterized lung cancer lncRNA polymorphisms with lung cancer susceptibility and platinum-based chemotherapy response. *Tumour Biol*. **37**, 8349–8358.

Guo Q. Y., Wang H. and Wang Y. 2017 LncRNA H19 polymorphisms associated with the risk of OSCC in Chinese population. *Eur. Rev. Med. Pharmacol. Sci*. **21**, 3770–3774.

Gyvyte U., Kupcinskas J., Juzenas S., Inciuraite R., Poskiene, L., Salteniene V. *et al.* 2018 Identification of long intergenic non-coding RNAs (lincRNAs) deregulated in gastrointestinal stromal tumors (GISTs). *PLoS One* **13**, e0209342.

Hashemi M., Bahari G., Naderi M., Sadeghi Bojd S. and Taheri M. 2016 Association of lnc-LAMC2-1:1 rs2147578 and CASC8 rs10505477 polymorphisms with risk of childhood acute lymphoblastic leukemia. *Asian Pac. J. Cancer Prev*. **17**, 4985–4989.

Hashemi M., Bahari G., Tabasi F., Moazeni-Roodi A. and Ghavami S. 2018 Association between rs1862513 and rs3745367 genetic polymorphisms of resistin and risk of cancer: a meta-analysis. *Asian Pac. J. Cancer Prev*. **19**, 2709–2716.

Hassanzarei S., Hashemi M., Sattarifard H., Hashemi S. M. and Bahari G. 2017 Genetic polymorphisms in long noncoding RNA H19 are associated with breast cancer susceptibility in Iranian population. *Meta Gene* **14**, 1–5.

He T. D., Xu D., Sui T., Zhu J. K., Wei Z. X. and Wang Y. M. 2017 Association between H19 polymorphisms and osteosarcoma risk. *Eur. Rev. Med. Pharmacol. Sci*. **21**, 3775–3780.

Hu P. H., Qiao O., Wang J., Li J., Jin H., Li Z. L. *et al.* 2017 rs1859168 A > C polymorphism regulates HOTTIP expression and reduces risk of pancreatic cancer in a Chinese population. *World J. Surg. Oncol*. **15**, 155.

Hua Q., Lv X., Gu X., Chen Y., Chu H., Du M. *et al.* 2016 Genetic variants in lncRNA H19 are associated with the risk of bladder cancer in a Chinese population. *Mutagenesis* **31**, 531–538.

Iyer M. K., Niknafs Y. S., Malik R., Singhal U., Sahu A., Hosono Y. *et al.* 2015 The landscape of long noncoding RNAs in the human transcriptome. *Nat. Genet*. **47**, 199–208.

Jiang Y., Qin Z., Hu Z., Guan X., Wang Y., He Y. *et al.* 2012 Genetic variation in a hsa-let-7 binding site in RAD52 is associated with breast cancer susceptibility. *Carcinogenesis* **34**, 689–693.

Jin T., Wu X., Yang H., Liu M., He Y., He X. *et al.* 2016 Association of the miR-17-5p variants with susceptibility to cervical cancer in a Chinese population. *Oncotarget* **7**, 76647–76655.

Li L., Guo G., Zhang H., Zhou B., Bai L., Chen H. *et al.* 2018 Association between H19 SNP rs217727 and lung cancer risk in a Chinese population: a case control study. *BMC Med. Genet*. **19**, 136.

Li S., Hua Y., Jin J., Wang H., Du M., Zhu L. *et al.* 2016 Association of genetic variants in lncRNA H19 with risk of colorectal cancer in a Chinese population. *Oncotarget* **7**, 25470–25477.

Li X. F., Yin X. H., Cai J. W., Wang M. J., Zeng Y. Q., Li, M. *et al.* 2017a. Significant association between lncRNA H19 polymorphisms and cancer susceptibility: a meta-analysis. *Oncotarget* **8**, 45143–45153.

Li Z., Li Y., Li Y., Ren K., Li X., Han X. *et al.* 2017b Long non-coding RNA H19 promotes the proliferation and invasion of breast cancer through upregulating DNMT1 expression by sponging miR-152. *J. Biochem. Mol. Toxicol*. **31**, e21933.

Li Z. and Niu Y. 2019 Association between lncRNA H19 (rs217727, rs2735971 and rs3024270) polymorphisms and the risk of bladder cancer in Chinese population. *Minerva. Urol. Nefrol.* **71**, 161–167.

Lichtenstein P., Holm N. V., Verkasalo P. K., Iliadou A., Kaprio J., Koskenvuo M. *et al.* 2000 Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. *N. Engl. J. Med*. **343**, 78–85.

Lv Z., Xu Q. and Yuan Y. 2017 A systematic review and meta-analysis of the association between long non-coding RNA polymorphisms and cancer risk. *Mutat. Res*. **771**, 1–14.

Matouk I. J., DeGroot N., Mezan S., Ayesh S., Abu-lail R., Hochberg A. *et al.* 2007 The H19 non-coding RNA is essential for human tumor growth. *PLoS One* **2**, e845.

Moazeni-Roodi A. and Hashemi M. 2018 Association between miR-124-1 rs531564 polymorphism and risk of cancer: an updated meta-analysis of case-control studies. *EXCLI J*. **17**, 608–619.

Quaye L., Tyrer J., Ramus S. J., Song H., Wozniak E., DiCioccio R. A. *et al.* 2009 Association between common germline genetic variation in 94 candidate genes or regions and risks of invasive epithelial ovarian cancer. *PLoS One* **4**, e5983.

Song H., Ramus S. J., Kjaer S. K., DiCioccio R. A., Chenevix-Trench G., Pearce C. L. *et al.* 2009 Association between invasive ovarian cancer susceptibility and 11 best candidate SNPs from breast cancer genome-wide association study. *Hum. Mol. Genet*. **18**, 2297–2304.

Verhaegh G. W., Verkleij L., Vermeulen S. H., den Heijer M., Witjes J. A. and Kiemeney L. A. 2008 Polymorphisms in the H19 gene and the risk of bladder cancer. *Eur. Urol*. **54**, 1118–1126.

Wang L., Cai Y., Zhao X., Jia X., Zhang J., Liu J. *et al.* 2015 Down-regulated long non-coding RNA H19 inhibits carcinogenesis of renal cell carcinoma. *Neoplasma* **62**, 412–418.

Xia T., Liao Q., Jiang X., Shao Y., Xiao B., Xi Y. *et al.* 2014 Long noncoding RNA associated-competing endogenous RNAs in gastric cancer. *Sci. Rep*. **4**, 6088.

Xia Z., Yan R., Duan F., Song C., Wang P. and Wang K. 2016 Genetic polymorphisms in long noncoding RNA H19 are associated with susceptibility to breast cancer in Chinese population. *Medicine (Baltimore)*. **95**, e2771.

Xue M., Zhuo Y. and Shan B. 2017 MicroRNAs, long noncoding RNAs, and their functions in human disease. *Methods Mol. Biol*. **1617**, 1–25.

Yang C., Tang R., Ma X., Wang Y., Luo D., Xu Z. *et al.* 2015 Tag SNPs in long non-coding RNA H19 contribute to susceptibility to gastric cancer in the Chinese Han population. *Oncotarget* **6**, 15311–15320.

Yang M. L., Huang Z., Wang Q., Chen H. H., Ma S. N., Wu R. *et al.* 2018 The association of polymorphisms in lncRNA-H19 with hepatocellular cancer risk and prognosis. *Biosci. Rep*. **38**, BSR20171652

Yin Z., Cui Z., Li H., Li J. and Zhou B. 2018 Polymorphisms in the H19 gene and the risk of lung Cancer among female never smokers in Shenyang, China. *BMC Cancer* **18**, 893.

Yu L. L., Chang K., Lu L. S. Zhao D., Han J., Zheng Y. R. *et al.* 2013 Lentivirus-mediated RNA interference targeting the H19 gene inhibits cell proliferation and apoptosis in human choriocarcinoma cell line JAR. *BMC Cell Biol*. **14**, 26.

Yuan Z., Yu Y., Zhang B., Miao L., Wang L., Zhao K. *et al.* 2018 Genetic variants in lncRNA H19 are associated with the risk of oral squamous cell carcinoma in a Chinese population. *Oncotarget* **9**, 23915.

Zhou X., Ye F., Yin C., Zhuang Y., Yue G. and Zhang G. 2015 The interaction between MiR-141 and lncRNA-H19 in regulating cell proliferation and migration in gastric cancer. *Cell Physiol. Biochem*. **36**, 1440–1452.

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