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Significant association between long non-coding RNA H19 polymorphisms and cancer susceptibility

A PRISMA-compliant meta-analysis and bioinformatics prediction

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Abstract

Background: H19, a well-known long non-coding RNA, is involved in carcinogenesis and progression of multiple cancers. Molecular epidemiological research suggests that polymorphisms in H19 are associated with an increased risk of cancer, but the results are inconsistent. Thus, we performed a meta-analysis to estimate the associations between H19 polymorphisms and cancer susceptibility.

Methods: PubMed, Embase, and Web of Science databases were searched. Odds ratios with 95% confidence interval were applied to assess the association between H19 rs2107425, rs217727, rs2839698, rs2735971, rs3024270, and rs3741219 polymorphisms and cancer susceptibility in all 5 models. We also predicted the H19 secondary structure, as well as the generation and abolishment of miRNA binding sites on H19 through the selected SNPs.

Results: Eighteen related studies, involving 17,090 patients and 23,532 control samples, were analyzed. The pooled data showed that rs2839698 polymorphism was significantly associated with an increased cancer susceptibility. As for rs217727 and rs3024270 polymorphisms, similarly increased risks were found in specific genetic models and stratified groups. However, significant decreases in cancer risk were observed for rs2107425 and rs2735971 in the total population, as well as in subgroup analyses. In addition, no significant associations were found in all 5 models for rs3741219 polymorphism. Furthermore, RNAfold prediction revealed that the centroid secondary structure was markedly altered in rs217727 and rs2735971. We also identified that rs217727 G>A and rs2839689 G>A alleles could create and destroy miRNA binding sites on H19.

Conclusion: The results of our meta-analyses suggest that H19 polymorphisms may be associated with the risk of cancer development.

Abbreviations: CI = confidence interval, HWE = Hardy-Weinberg equilibrium, lncRNA = long non-coding RNA, MFE = minimum free energy, NOS = Newcastle Ottawa Scale, ORs = odds ratios, SNP = single nucleotide polymorphism.

Keywords: cancer susceptibility, H19, meta-analysis, polymorphisms, secondary structure

1. Introduction

Cancer is the leading cause of morbidity and mortality worldwide.[1] In 2012, approximately 14 million people were diagnosed with cancer, 8.2 million of these patients died due to this disease, and most of these patients belonged to impoverished nations.[2] Generally, cancers are considered as multifactorial diseases, and their onset is related to genetic, environmental, and lifestyle factors. Currently, there are many molecular epidemiological studies demonstrating that genetic factors may play an essential role in cancer development, and genetic susceptibility trait is attracting increasing attention.[3] Recently, genome-wide association studies and next-generation sequencing technology have markedly broadened our understanding of the genetic variations that confer risks for cancers.

Long non-coding RNAs (lncRNAs), which were first identified in the 1990 s, are single-stranded, non-coding RNAs with lengths of more than 200 nucleotides without open reading frames.[4] Various lncRNAs are known to play a role in various diseases, including cancers, via transcriptional and post-transcriptional regulation of the expression of oncogenes or tumor suppressors.[5] lncRNAs are involved in many cellular processes, such as differentiation, proliferation, apoptosis, metabolism, and autophagy,[6–10] being also important regulators of tissue pathology and cancerogenesis.[3]

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The lncRNA H19, located on human chromosome 11p15.5 with a length of 3.0 kb, belongs to the lncRNA family, which comprises mRNA-like transcripts, lacking an open reading frame.[11] Many studies have confirmed that H19 is re-expressed in many types of solid tumors, such as breast cancer, gastric cancer, and esophageal cancer, and H19 expression is closely related to tumor invasion, metastasis, recurrence, and poor prognosis.[12,13] Recently, a meta-analysis performed by Chen et al has shown that overexpression of H19 may be regarded as a predictive indicator of poor prognoses in multiple cancers. Other studies have also demonstrated that a high expression of H19 is significantly associated with lymph node metastasis and with other processes, affecting tumor prognosis.[14]

Genetic variants, mainly including single nucleotide polymorphisms (SNPs), have been confirmed to affect susceptibility to cancers in various organs. However, a large number of these SNPs are not located within the protein coding genes, but rather within the noncoding regions. In recent years, the SNPs of lncRNA genes have been widely confirmed to regulate the expression and function of lncRNAs, leading to the emergence of tumor susceptibility and poor prognosis signature.[15,16] Previous studies have identified associations between the 3 most common SNPs in H19 (rs2839698 G>A, rs217727 G>A, and rs2107425 C>T) and cancer susceptibility. Li et al found that lncRNA H19 rs2839698 polymorphism A allele has a significantly increased risk of colorectal cancer, compared to the individuals carrying G allele.[17] Verhaegh et al found that the heterozygote H19 rs2839698 polymorphism might be associated with bladder cancer risk in a Caucasian population.[18] However, some results are controversial. The lncRNA H19 rs217727 polymorphism has been shown to be associated with susceptibility to gastric cancer, breast cancer, and bladder cancer in the Chinese population.[19–21] On the other hand, Verhaegh et al showed that the rs217727 polymorphism might not be associated with bladder cancer in a Caucasian population, even if the subjects are grouped by tumor stage or grade.[18] Moreover, Hu et al found that rs217727 has no association with pancreatic cancer risk in the Chinese population.[22] Subsequent studies, investigating the association between the lncRNA H19 polymorphisms and cancer susceptibility, have reported inconsistent results. Thus, we performed a comprehensive meta-analysis, involving the related studies, to assess the possible association between H19 polymorphisms and cancer susceptibility.

2. Materials and methods

The presented herein meta-analysis was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] Ethical approval was not required for this systematic review and meta-analysis owing to unnecessary data connected with individual patient information.

2.1. Literature search

The PubMed, Embase and Web of Science databases were searched for relevant studies that examined the association between H19 polymorphisms and cancer susceptibility prior to April 30, 2018. The following search terms were used: "H19 or long Noncoding RNA H19 or lncRNA H19," "cancer or carcinoma or tumor or neoplasm," "polymorphism or variation or variant or mutation or SNP." Only available full-text articles, written in English, were included in this meta-analysis. Moreover, citation lists of all relevant articles were manually searched for additional eligible publications.

2.2. Eligibility criteria

All selected studies had to meet the following criteria:

(1) studies based on case-control design, assessing the association between the H19 polymorphisms and cancer susceptibility;
(2) studies including sufficient genotype distribution data to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

The exclusion criteria were as follows:

(1) abstract, comment, and review as publication type;
(2) duplication of the previous reports;
(3) lack of usable genotype frequency data.

2.3. Data extraction

Two independent investigators (Wei Li and XiaoJing Jin) extracted the following relevant information from the included studies: first author name, publication year, ethnicity and country of origin, sources of controls, genotyping method, case-control matched status, the type of studied cancer, minor allele frequency, Hardy-Weinberg equilibrium (HWE) status of controls, number of genotypes in cancer cases and controls, and article quality. Any disagreement was resolved through the discussion, until the 2 reviewers reached a consensus.

2.4. Quality assessments of the included studies

Two reviewers (WeiTao Yan and DongYun Li) independently assessed the quality of the included studies, according to the Newcastle Ottawa Scale (NOS). Using this method, each study was evaluated on standard criteria and subsequently categorized, based on 3 factors: selection, comparability, and exposure. The scores ranged from 0 points (worst) to 10 points (best).

2.5. Statistical analysis

The risk of cancer, associated with each H19 polymorphism, was estimated in each study using the OR and its 95% confidence interval (95% CI). For the H19 rs2107425 C>T polymorphism, the pooled ORs were obtained for allele (T vs C), recessive (TT vs TC + CC), dominant (TC + TT vs CC), heterozygous (TC vs CC) and homozygous (TT vs CC). Similar genetic models were also assessed for H19 rs217727 G>A and rs2839698 G>A variants. The Cochran Q test and I^2 statistic were used to evaluate the heterogeneity between studies. For P value in Q test $\leq .05$ or $I^2 \geq 50\%$, significant heterogeneity was considered and the random-effects model was applied. Otherwise, the fixed-effects model was used. Subgroup analyses were performed based on ethnicity, source of controls, genotyping methods, type of cancers, and HWE status of controls. Sensitivity analyses were performed to examine the stability of the results by excluding the studies 1-by-1. Funnel plot Egger tests were applied to detect the potential publication bias. Data were analyzed and processed using Review Manager 5.3 (Cochrane Informatics and Knowledge Management Department) and Stata 12.0 (StataCorp LP, College Station, TX). $P \leq .05$ was considered as statistically significant.

2.6. Ethical approval

This meta-analysis was performed based on the previous studies. So, the ethical approval was not required.

3. Results

3.1. Characteristics of the published studies

The study selection process is shown in Figure 1. A total of 26 articles, reporting on relationship between H19 SNPs and cancer risk, were retrieved after first search in PubMed, Embase and Web of Science databases. At the end of the gradual selection process, eighteen published reports, involving a total of 17090 cancer patients and 23532 healthy controls, met our inclusion criteria and were included in this meta-analysis.[17–22,24–35] These reports on the association of H19 polymorphisms with cancer susceptibility were distributed by cancer type as follows: breast cancer (n=6); bladder cancer (n=2); ovarian cancer (n=2); gastric cancer (n=1); lung cancer (n=1); colorectal cancer (n=1); pancreatic cancer (n=1); oral squamous cell carcinoma (n=1); osteosarcoma (n=1); cervical cancer (n=1); and hepatocellular carcinoma (n=1). There are 7 studies available for rs2107425 C>T polymorphism,[18,24–26,31–33] eleven studies for rs217727 G>A polymorphism,[17–22,27–30,35] 10 studies for rs2839698 G>A polymorphism,[17–20,26–30,34] 5 studies for rs2735971 C>T polymorphism,[17,19,27,29,34] 5 studies for rs3024270 G>C polymorphism,[17,19,27,29,34] and 3 studies for rs3741219 T>C polymorphism.[20,21,28] The characteristics of the included studies are presented in Table 1. Assessment of NOS scale in each study showed that all the studies were of high quality (Table 2).

3.2. Association between the H19 rs2107425 C>T polymorphism and cancer susceptibility

A total of 7 related studies, including 10974 cases and 15616 controls, were examined for the association between the H19 rs2107425 C>T polymorphism and cancer susceptibility. The variant T allele of rs2107425 was correlated with a significantly decreased risk of developing cancer (allelic model (T vs C): OR = 0.95, 95% CI = 0.92–0.99, $P = .01$, $I^2 = 42\%$; Table 3). Next, we evaluated the effect of the rs2107425 polymorphism on cancer susceptibility among the subgroups. The same association with decreased risk was observed in Caucasian populations by race (allelic model [T vs C]: OR = 0.95, 95% CI = 0.91–0.99, $P = .01$, $I^2 = 52\%$), and in studies with population-based controls (allelic

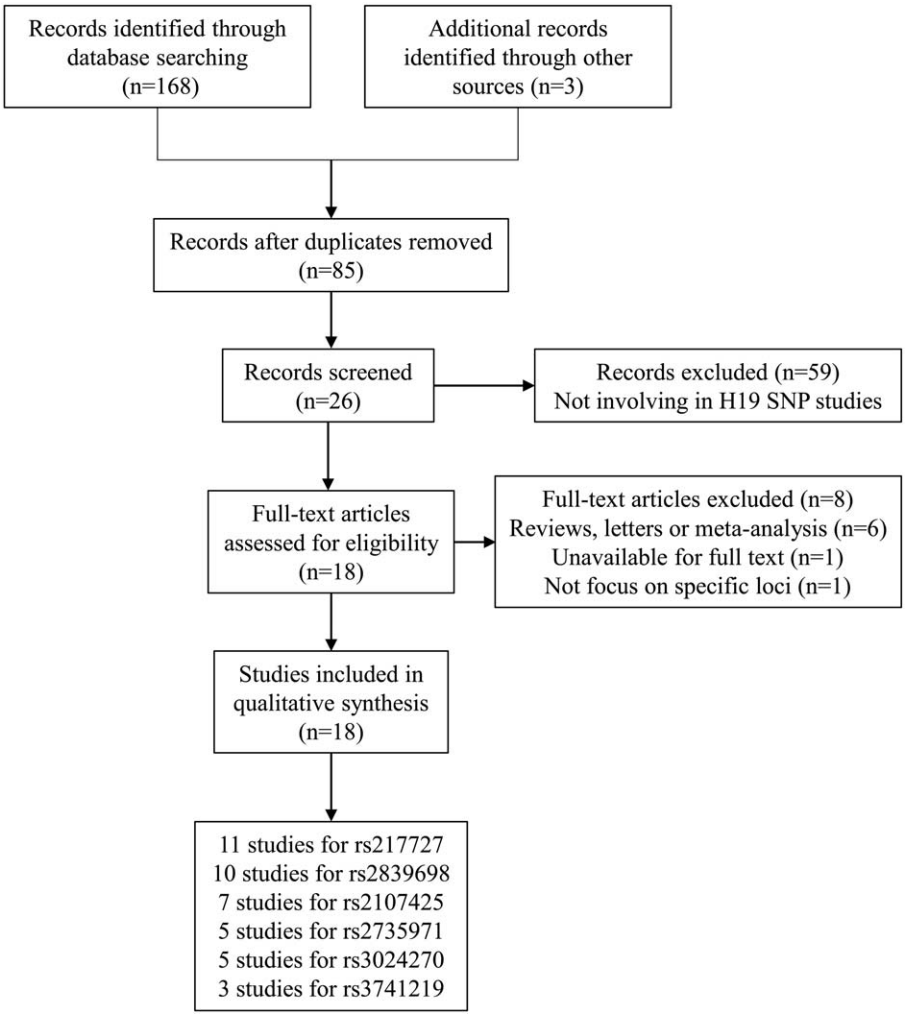

Figure 1. Flow diagram of the study selection process.

Table 1

Characteristics of included studies on lncRNA H19 polymorphisms and cancer susceptibility included in the meta-analysis.

Author	Yr	Cancer type	Country	Ethnicity	Source of controls	platform	Case/Control	Case			Control			MAF in control	*P* for HWE[a]	NOS
							rs2107425 C>T	CC	CT	TT	CC	CT	TT			
Butt	2012	Breast	Sweden	Caucasian	PB	Sequenom	679/1386	361	250	68	668	573	145	0.31	.18	8
Barnholtz	2010	Breast	USA	Caucasian	PB	GoldenGate	1962/1776	765	906	291	691	817	268	0.38	.3	7
Bhatti	2008	Breast	USA	Caucasian	PB	Sequenom	824/1073	392	432	502	571	NA	NA	8		
Song	2009	Ovarian	Mixed[b]	Caucasian	PB	TaqMan	5366/8538	2619	2192	555	4029	3667	842	0.31	.86	7
Verhaegh	2008	Bladder	Netherland	Caucasian	PB	PCR-PFLP	204/177	89	96	19	92	65	20	0.3	.11	9
Gong	2016	Lung	China	Asian	HB	Sequenom	479/203	181	235	63	79	96	28	0.37	.89	6
Quaye	2009	Ovarian	Mixed[c]	Caucasian	PB	TaqMan	1460/2463	767	544	149	1118	1098	247	0.32	.34	6
							rs217727 G>A	GG	GA	AA	GG	GA	AA			
Guo	2017	OCSS	China	Asian	HB	Illumina	362/741	133	171	58	244	377	120	0.42	.2	8
He	2017	OS	China	Asian	HB	TaqMan	193/383	79	102	12	195	165	23	0.28	.12	6
Hu	2017	Pancreatic	China	Asian	HB	TaqMan	416/416	133	200	83	128	196	92	0.46	.3	7
Li	2016	Colorectal	China	Asian	HB	TaqMan	1147/1203	480	514	153	456	570	177	0.38	.96	8
Hassanzarei	2017	Breast	Iranian	Asian	HB	PCR-RFLP	230/240	71	132	27	125	113	2	0.24	< .01	7
Xia	2016	Breast	China	Asian	PB	CRS-RFLP	464/467	160	156	148	139	212	116	0.48	.052	9
Hua	2016	Bladder	China	Asian	HB	TaqMan	1046/1394	431	467	148	573	665	156	0.35	.074	7
Lin	2017	Breast	China	Asian	HB	G0104K	1005/1020	403	471	131	465	450	105	0.32	.8	8
Verhaegh	2008	Bladder	Netherland	Caucasian	PB	PCR-PFLP	177/204	114	59	4	115	80	9	0.24	.29	9
Yang	2015	Gastric	China	Asian	HB	TaqMan	500 /500	160	252	88	193	244	63	0.37	.3	8
Jin	2016	Cervical	China	Asian	HB	Sequenom	246/284	117	103	26	169	99	16	0.231	.74	6
							rs2839698 G>A	GG	GA	AA	GG	GA	AA			
Guo	2017	OSCC	China	Asian	HB	Illumina	362/741	133	171	58	244	377	120	0.42	.2	8
He	2017	OS	China	Asian	HB	TaqMan	193/383	83	98	12	178	175	30	0.31	.15	6
Li	2016	Colorectal	China	Asian	HB	TaqMan	1147/1203	583	462	102	666	462	75	0.25	.67	8
Gong	2016	Lung	China	Asian	HB	Sequenom	496/206	237	220	39	99	80	27	0.33	.098	6
Hassanzarei	2017	Breast	Iranian	Asian	HB	PCR-RFLP	230/240	166	64	0	222	18	0	0.04	.55	7
Hua	2016	Bladder	China	Asian	HB	TaqMan	1049/1397	552	418	79	729	565	103	0.28	.65	7
Lin	2017	Breast	China	Asian	HB	G0104K	1005/1020	452	440	113	484	432	104	0.31	.6	8
Verhaegh	2008	Bladder	Netherland	Caucasian	PB	PCR-PFLP	177/204	54	74	49	52	109	43	0.48	.31	9
Yang	2015	Gastric	China	Asian	HB	TaqMan	500 /500	250	195	55	284	178	38	0.254	.18	8
Yang	2018	HCC	China	Asian	HB	KASP	466/462	215	211	40	245	185	32	0.269	.297	8
							rs2735971 C>T	CC	CT	TT	CC	CT	TT			
Guo	2017	OSCC	China	Asian	HB	Illumina	461/739	191	141	129	351	308	80	0.316	.315	8
He	2017	OS	China	Asian	HB	TaqMan	193/383	88	94	11	169	182	32	0.321	.08	6
Hua	2016	Bladder	China	Asian	HB	TaqMan	1049/1396	704	302	43	928	422	46	0.18	.815	7
Li	2016	Colorectal	China	Asian	HB	TaqMan	1147/1203	773	334	40	765	398	40	0.199	.175	8
Yang	2018	HCC	China	Asian	HB	KASP	465/465	327	126	12	313	139	13	0.177	.697	8
							rs3024270 G>C	GG	GC	CC	GG	GC	CC			
Guo	2017	OSCC	China	Asian	HB	Illumina	362/740	104	183	75	245	350	145	0.432	.321	8
He	2017	OS	China	Asian	HB	TaqMan	193/383	85	91	17	173	179	31	0.315	.1	6
Hua	2016	Bladder	China	Asian	HB	TaqMan	1047/1395	346	527	174	447	688	260	0.433	.868	7
Li	2016	Colorectal	China	Asian	HB	TaqMan	1147/1203	385	527	235	420	582	201	0.409	.979	8
Yang	2018	HCC	China	Asian	HB	KASP	471/466	151	225	95	170	215	81	0.406	.247	8
							rs3741219 T>C	TT	TC	CC	TT	TC	CC			
Yang	2015	Gastric	China	Asian	HB	TaqMan	500 /500	260	187	53	268	189	43	0.275	.245	8
Xia	2016	Breast	China	Asian	PB	CRS-RFLP	464/467	238	186	40	245	182	40	0.292	.456	9
Hassanzarei	2017	Breast	Iranian	Asian	HB	PCR-RFLP	231/240	63	126	42	109	102	29	0.333	.5	7

[a] HWE in control.

[b] including European countries, USA and Australia.

[c] including UK, Denmark and USA.

CRS-RFLP = created restriction site-restriction fragment length polymorphism, HB = hospital-based, HWE = Hardy-Weinberg equilibrium, MAF = minor allele frequency in control group, NOS = Newcastle Ottawa Scale, PB = population-based.

model (T vs C): OR = 0.95, 95% CI = 0.91–0.99, $P = .01$, $I^2 = 52\%$) in the subgroup analyses (Table 3).

3.3. Association between the H19 rs217727 G>A polymorphism and cancer susceptibility

A total of eleven relevant studies, consisting of 5786 patients and 6852 controls, were examined for the association between the H19 rs217727 G>A polymorphism and cancer susceptibility. No significant overall associations were found in any of the 5 genetic models. Further stratified analyses revealed that rs217727 SNP was significantly associated with decreased cancer risk among studies with population-based controls (dominant model [GA +AA vs GG]: OR = 0.78, 95% CI = 0.62–0.98, $P = .03$, $I^2 = 0$; heterozygous model [GA vs GG]: OR = 0.67, 95% CI = 0.53–0.86, $P = .002$, $I^2 = 0$; Table 4). In contrast, significant

Table 2

Summary of the quality assessment using the Newcastle-Ottawa scale for case-control studies.

		Selection				Comparability		Exposure			
Studies	Year	Case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Adjustment for age	Adjustment for lifestyle/traditional risk factors	Ascertainment of exposure	Uniform Method of ascertainment	Non-response rate	Total quality score
Butt	2012	1	1	1	1	1	1	1	1	0	8
Barnholtz	2010	1	1	1	1	1	0	1	1	0	7
Bhatti	2008	1	1	1	1	1	1	1	1	0	8
Song	2009	1	1	1	1	1	0	1	1	0	7
Verhaegh	2008	1	1	1	1	1	1	1	1	1	9
Gong	2016	1	1	0	1	1	0	1	1	0	6
Quaye	2009	1	1	1	1	0	0	1	1	0	6
Jin	2016	1	1	0	1	1	0	1	1	0	6
Guo	2017	1	1	0	1	1	1	1	1	1	8
He	2017	1	1	0	1	1	0	1	1	0	6
Hu	2017	1	1	0	1	1	1	1	1	0	7
Li	2016	1	1	0	1	1	1	1	1	1	8
Hassanzarei	2017	1	1	0	1	1	0	1	1	1	7
Xia	2016	1	1	1	1	1	1	1	1	1	9
Hua	2016	1	1	0	1	1	1	1	1	0	7
Lin	2017	1	1	0	1	1	1	1	1	1	8
Yang	2018	1	1	0	1	1	1	1	1	1	8
Yang	2015	1	1	0	1	1	1	1	1	1	8

correlations with increased cancer risk were observed in the Asian populations (allelic model (A vs G): OR = 1.16, 95% CI = 1.01–1.32, $P = .03$, $I^2 = 82\%$; recessive model (AA vs GG +GA): OR = 1.25, 95% CI = 1.01–1.53, $P = .04$, $I^2 = 69\%$), and in breast cancer (allelic model (A vs G): OR = 1.15, 95% CI = 1.03–1.27, $P = 0.01$, $I^2 = 29\%$; recessive model (AA vs GG+GA): OR = 1.36, 95% CI = 1.11–1.65, $P < .01$, $I^2 = 0$; homozygous model (AA vs GG): OR = 1.29, 95% CI = 1.03–1.60, $P = .02$, $I^2 = 26\%$) when the studies restricted to HWE (Table 4).

3.4. Association between the H19 rs2839698 G>A polymorphism and cancer susceptibility

A total of 10 relevant studies, consisting of 5625 patients and 6356 controls, were examined for the association between the H19 rs2839698 G>A polymorphism and cancer susceptibility. The variant A allele of rs2839698 was correlated with a significantly increased risk of developing cancer (allelic model (A vs G): OR = 1.13, 95% CI = 1.00–1.28, $P = .05$, $I^2 = 76\%$; recessive model (AA vs GG+GA): OR = 1.13, 95% CI = 1.00–1.29, $P = .05$, $I^2 = 45\%$; homozygous model (AA vs GG): OR = 1.15, 95% CI = 1.00–1.31, $P = .04$, $I^2 = 47\%$; (Fig. 2). Next, we evaluated the effect of the rs2839698 polymorphism on cancer risk among the subgroups (Table 5). The rs2839698 SNP had significant association with increased cancer risk in the Asian populations and hospital-based controls subgroup (allelic model [A vs G]: OR = 1.14, 95% CI = 1.00–1.31, $P = .05$, $I^2 = 79\%$; dominant model [GA+AA vs GG]: OR = 1.20, 95% CI = 1.01–1.43, $P = .03$, $I^2 = 78\%$; heterozygous model (GA vs GG): OR = 1.20, 95% CI = 1.01–1.44, $P = .04$, $I^2 = 77\%$). Moreover, elevated risks of Taqman-method subgroup (allelic model [A vs G]: OR = 1.12, 95% CI = 1.03–1.21, $P < .01$, $I^2 = 56\%$; recessive model [AA vs GG+GA]: OR = 1.23, 95% CI = 1.02–1.48, $P = .03$, $I^2 = 42\%$; dominant model [GA+AA vs GG]: OR = 1.12, 95% CI = 1.02–1.24, $P = .02$, $I^2 = 38\%$; homozygous model [AA vs GG]: OR = 1.28, 95% CI = 1.06–1.55, $P = .01$, $I^2 = 50\%$) were detected. Beyond that, subgroup analyses by cancer type indicated that rs2839698 G>A was associated with an increase in digestive cancer risk (allelic model [A vs G]: OR = 1.15, 95% CI = 1.00–1.32, $P = .05$, $I^2 = 62\%$; recessive model [AA vs GG+GA]: OR = 1.28, 95% CI = 1.06–1.54, $P < .01$, $I^2 = 14\%$; homozygous model (AA vs GG): OR = 1.33, 95% CI = 1.10–1.62, $P < .01$, $I^2 = 52\%$; heterozygous model [GA vs GG]: OR = 1.13, 95% CI = 1.00–1.26, $P = .04$, $I^2 = 52\%$).

3.5. Association between the H19 rs2735971 C>T, rs3024270 G>C or rs3741219 T>C polymorphisms and cancer susceptibility

In general, a significant association of rs2735971 polymorphism with decreased cancer risk in heterozygous model (CT vs CC: OR = 0.88, 95% CI = 0.80–0.98, $P = .02$, $I^2 = 0$; Table 3) was detected. In subgroup analysis, rs2735971 showed a significant decreased risk of cancer in heterozygous model in digestive cancer (CT vs CC: OR = 0.84, 95% CI = 0.74–0.96, $P = .01$, $I^2 = 0$). Analysis of rs3024270 showed a significantly increased cancer risk in dominant model (GC+CC vs GG: OR = 1.14, 95% CI = 1.03–1.25, $P = .01$, $I^2 = 0$; Table 5), but not in other genetic models. In subgroup analysis, evaluation of rs3024270 impact demonstrated a significantly increased risk of digestive cancer (allelic model [C vs G]: OR = 1.12, 95% CI = 1.03–1.22, $P < .01$, $I^2 = 0$; recessive model [CC vs GG+GC]: OR = 1.21, 95% CI = 1.04–1.41, $P = .01$, $I^2 = 0$; homozygous model (CC vs GG): OR = 1.27, 95% CI = 1.07–1.51, $P < .01$, $I^2 = 0$). No significant associations were found in all 5 models for rs3741219 polymorphism (Table 4).

3.6. Sensitivity analysis and publication bias

Sensitivity analysis showed that the pooled ORs were not substantially influenced by any single study in all 5 genetic models for corresponding SNP sites, indicating that our results were

Table 3

Summary ORs and 95% CIs of H19 rs2107425 and rs2735971 polymorphisms and cancer susceptibility.

Locus	Studies	Case/Control	OR	95%CI	P[a]	I^2(%)[b]	OR	95%CI	P	I^2(%)	OR	95%CI	P	I^2(%)	OR	95%CI	P	I^2(%)	OR	95%CI	P	I^2(%)
rs2107425 C>T			T vs C				(CT+TT) vs CC				TT vs (CC+CT)				TT vs CC				CT vs CC			
Total	7	10974/15616	0.95	0.92–0.99	.01	42	0.92	0.83–1.03	.13	66	1.02	0.94–1.11	.67	0	0.96	0.88–1.05	.36	0	0.92	0.80–1.05	.22	75
Ethnicity																						
Caucasian	6	10495/15413	0.95	0.91–0.99	.01	52	0.92	0.82–1.02	.12	71	1.02	0.94–1.11	.63	0	0.96	0.88–1.05	.36	4	0.9	0.78–1.05	.18	79
Design																						
PB	6	10495/15413	0.95	0.91–0.99	.01	52	0.92	0.82–1.02	.12	71	1.02	0.94–1.11	.63	0	0.96	0.88–1.05	.36	4	0.9	0.78–1.05	.18	79
Platform																						
Sequenom	3	1982/2662	0.91	0.81–1.03	.14	0	0.91	0.81–1.03	.13	16	0.95	0.74–1.23	.7	0	0.8	0.61–1.04	.09	0	0.86	0.73–1.02	.09	45
TaqMan	2	6826/11001	0.92	0.8–1.05	.2	83	0.84	0.68–1.05	.13	83	1.05	0.95–1.16	.37	0	0.98	0.89–1.09	.74	18	0.82	0.65–1.04	.1	89
rs2735971 C>T			T vs C				(CT+TT) vs CC				TT vs (CC+CT)				TT vs CC				CT vs CC			
Total	5	3315/4186	1.04	0.82–1.43	.75	89	0.96	0.89–1.05	.38	52	1.26	0.68–2.32	.46	87	1.22	0.68–2.17	.51	85	0.88	0.80–0.98	.02	0
Cancer type																						
digestive	3	2073/2407	1.10	0.72–1.67	.67	94	0.98	0.75–1.27	.86	76	1.52	0.63–3.66	.36	90	1.43	0.60–3.37	.42	89	0.84	0.74–0.96	.01	0

[a] *P*-values were obtained from *Z*-test.

[b] test for heterogeneity.

CI = confidence interval, OR = odds ratio, PB = population-based.

Table 4

Summary ORs and 95% CIs of H19 rs217727 and rs3741219 polymorphisms and cancer susceptibility.

Locus	Studies	Case/Control	OR	95%CI	P[a]	I^2(%)[b]	OR	95%CI	P	I^2(%)	OR	95%CI	P	I^2(%)	OR	95%CI	P	I^2(%)	OR	95%CI	P	I^2(%)
rs217727 G>A			A vs G				(GA+AA) vs GG				AA vs (GG+GA)				AA vs GG				GA vs GG			
Total	11	5786/6852	1.12	0.99,1.28	.08	82	1.11	0.93,1.33	.23	81	1.22	0.99,1.50	.06	68	1.24	0.96,1.60	.10	76	1.06	0.89,1.26	.5	78
Controls in HWE	10	5556/6612	1.07	0.96,1.19	.24	72	1.04	0.90,1.21	.59	73	1.17	0.99,1.37	.06	51	1.15	0.94,1.41	.18	63	1.00	0.86,1.17	.97	72
Ethnicity																						
Asian	10	5609/6648	1.16	1.01,1.32	.03	82	1.15	0.96,1.38	.12	82	1.25	1.01,1.53	.04	69	1.29	0.99,1.66	.06	77	1.09	0.91,1.30	.35	79
Asian(HWE)	9	5379/6408	1.09	0.98,1.21	.11	72	1.07	0.92,1.25	.38	74	1.18	1.01,1.38	.04	52	1.17	0.96,1.44	.11	63	0.99	0.84,1.16	.88	72
Design																						
HB	9	5145/6181	1.17	1.01,1.36	.03	84	1.20	0.99,1.45	.06	82	1.23	0.98,1.55	.08	71	1.33	0.99,1.78	.06	79	1.15	0.97,1.36	.12	76
PB	2	641/771	0.91	0.65,1.27	.58	67	0.78	0.62,0.98	.03	0	1.00	0.38,2.62	1.00	64	1.03	0.75,1.42	.84	50	0.67	0.53,0.86	.002	0
Platform																						
TaqMan	5	3302/3896	1.06	0.92,1.22	.43	73	1.07	0.88,1.29	.51	71	1.10	0.87,1.38	.42	58	1.11	0.84,1.48	.45	68	1.04	0.87,1.25	.64	65
Cancer type																						
Breast	3	1699/1727	1.35	0.98,1.87	.06	88	1.33	0.80,2.20	.28	91	1.83	1.02,3.28	.04	82	2.09	0.96,4.52	.06	88	1.16	0.66,2.02	.61	91
Breast(HWE)	2	1469/1487	1.15	1.03,1.27	.01	29	1.10	0.95,1.28	.2	86	1.36	1.11,1.65	< .01	0	1.29	1.03,1.60	.02	26	0.89	0.48,1.66	.71	92
Bladder	2	1223/1598	0.92	0.65,1.31	.65	73	0.95	0.82,1.11	.53	53	0.97	0.41,2.32	.95	58	0.90	0.34,2.33	.82	63	0.9	0.77,1.06	.21	0
Digestive	4	2425/2860	0.99	0.84,1.16	.90	73	0.97	0.78,1.19	.76	67	1.02	0.81,1.28	.88	53	1.00	0.73,1.38	.99	70	0.93	0.83,1.05	.27	50
rs3741219 T>C			C vs T				(TC+CC) vs TT				CC vs (TT+TC)				CC vs TT				TC vs TT			
Total	3	1195/1207	1.22	0.93,1.59	.15	78	1.32	0.88,1.98	.18	83	0.6	0.12,3.0	.53	98	1.45	0.89,2.35	.13	66	1.28	0.86,1.91	.22	80
Cancer type																						
breast	2	695/707	1.3	0.81,2.08	.27	88	1.5	0.72,3.13	.28	90	1.24	0.89,1.75	.21	45	1.58	0.66,3.79	.3	89	1.47	0.74,2.95	.27	88

[a] *P*-values were obtained from *Z*-test.

[b] test for heterogeneity.

CI = confidence interval, HB = hospital-based, HWE = Hardy-Weinberg equilibrium, OR = odds ratio, PB = population-based.

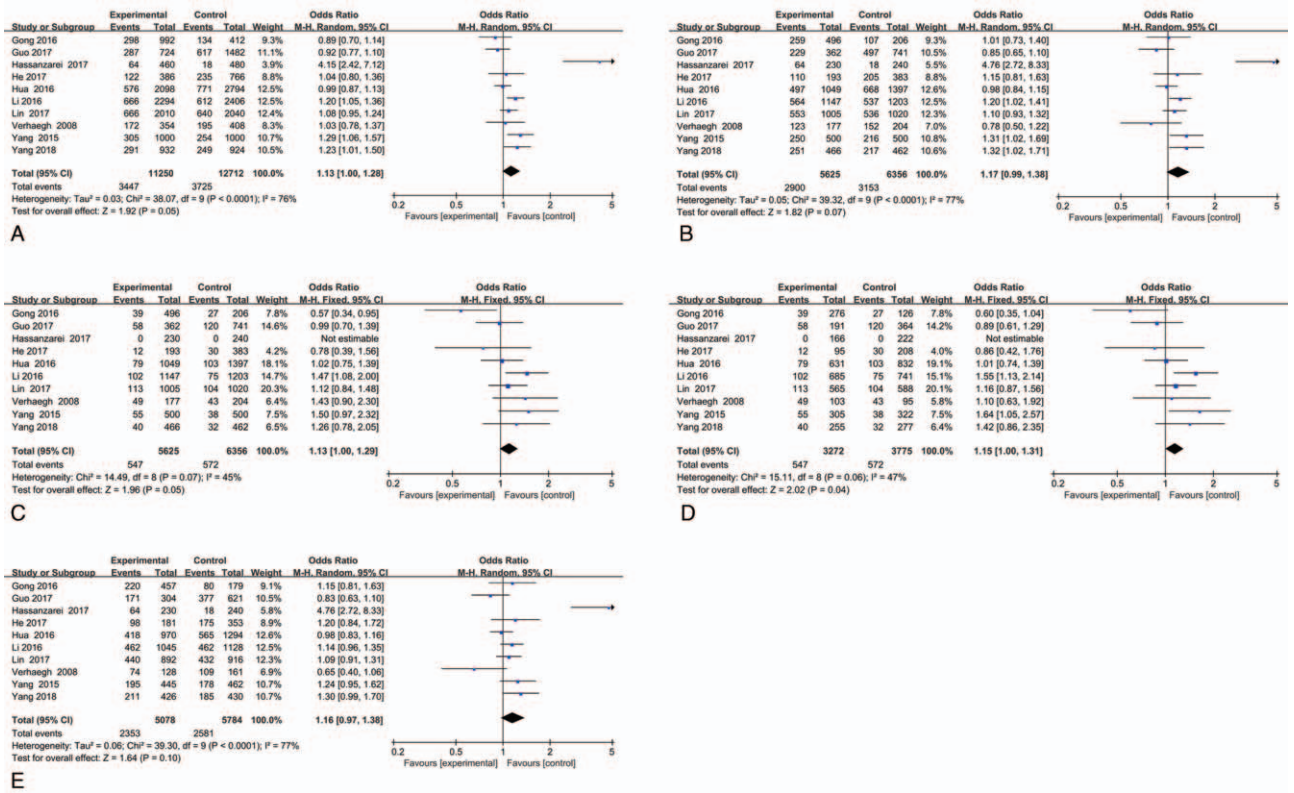

Figure 2. Forest plot for H19 rs2839698 polymorphism and cancer susceptibility. (A) allele model (A vs G); (B) dominant model (GA+AA vs GG); (C) recessive model (AA vs GG+GA); (D) homozygous model (AA vs GG); (E) heterozygous model (GA vs GG).

statistically robust (Fig. 3A). Visual inspection of funnel plot did not reveal any asymmetrical evidence (Fig. 3B). The results were further supported by the analysis of the data with Egger test.

3.7. Prediction of H19 polymorphisms centroid secondary structure and target microRNAs

RNAfold web server (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi/) was used to perform in silico analyses for the prediction of H19 secondary structure, harboring selected SNPs. Consequently, RNAfold prediction revealed that the centroid secondary structure was markedly changed with rs217727 G>A and rs2735971 C>T alleles (Fig. 4). The minimum free energy (MFE) of the rs217727 G>A alleles centroid secondary structure was changed from -56.30 kcal/mol to -58.30 kcal/mol. The MFE of the rs2735971 C>T alleles centroid secondary structure was also changed from -90.20 kcal/mol to -90.90 kcal/mol. However, there were few changes of the centroid secondary structure and MFE with rs3024270 G>C alleles, rs2839698 G>A alleles, and rs2107425 C>T alleles.

By using the lncRNA-binding prediction software program (http://bioinfo.life.hust.edu.cn/lncRNASNP2/), we found that the conversion of G>A in the 3′UTR rs2839689 polymorphism may create binding sites for hsa-miR-6894-3p, hsa-miR-4674, hsa-miR-6514-3p and hsa-miR-378 microRNAs (miRNAs) and destroy hsa-miR-24-1-5p, hsa-miR-24-2-5p, hsa-miR-4486 and hsa-miR-566 miRNA binding sites on H19. Furthermore, we predicted that hsa-miR-8072 and hsa-miR-3960 may fail to target H19 gene with rs217727 G>A alleles, following with the creating of binding site for hsa-miR-8071 and hsa-miR-4804–5p. Based on out prediction, there are no miRNAs that associate with the rs2107425 C>T alleles, rs2735971 C>T alleles, and rs3024270 G>C alleles.

4. Discussion

Cancer is a polygenic and multifactorial disease, which is thought to be caused by complex genetic factors and gene-environment interactions. lncRNAs participate in the diverse biological processes and abnormal expression of lncRNAs is associated with human cancers.[36,37] In several lncRNAs, SNPs have been confirmed to be related to carcinogenesis and associated with cancer susceptibility.[38,39] H19 is an imprinted gene, which is transcribed only from the maternal allele, and has been confirmed to be essential for carcinogenesis.[40,41] More than 2200 H19 SNPs can be found in the NCBI SNP database (https://www.ncbi.nlm.nih.gov/snp). In these polymorphisms, rs2107425, rs217727, rs2839698, rs2735971, rs3024270, and rs3741219 are the 6 major SNPs associated with tumor susceptibility. Verhaegh et al first examined H19 polymorphisms in 2008,[18] and a series of case-control studies have been conducted since then. Recently, several studies have been published to evaluate the relationship between SNPs of H19 and the cancer susceptibility, but the results were still contradictory.[17,18,20,21,27] However, due to the limited number of studies and small sample size involved, additional investigations are required to confirm these results.

Meta-analysis can be used to integrate data from multiple studies, thereby expanding sample size and increasing the

Table 5

Summary ORs and 95% CIs of H19 rs2839698 and rs3024270 polymorphisms and cancer susceptibility.

Locus	Studies	Case/Control	OR	95%CI	P^a	I^2(%)[b]	OR	95%CI	P	I^2(%)	OR	95%CI	P	I^2(%)	OR	95%CI	P	I^2(%)
rs2839698 G>A			A vs G				(GA+AA) vs GG				AA vs (GG+GA)				AA vs GG				GA vs GG			
Total	10	5625/6356	1.13	1.00,1.28	.05	76	1.17	0.99,1.38	.07	77	1.13	1.00,1.29	.05	45	1.15	1.00,1.31	.04	47	1.16	0.97,1.38	.10	77
Ethnicity																						
Asian	9	5448/6152	1.14	1.00,1.31	.05	79	1.20	1.01,1.43	.03	78	1.11	0.98,1.27	.11	48	1.13	0.91,1.39	.27	54	1.20	1.01,1.44	.04	77
Design																						
HB	9	5448/6152	1.14	1.00,1.31	.05	79	1.20	1.01,1.43	.03	78	1.11	0.98,1.27	.11	48	1.13	0.91,1.39	.27	54	1.20	1.01,1.44	.04	77
Platform																						
PCR-RFLP	2	407/444	2.03	0.52,7.97	.31	95	1.91	0.32,11.29	.48	96	NA	NA	NA	NA	1.75	0.25,12.20	.57	96				
TaqMan	4	2889/3483	1.12	1.03,1.21	< .01	56	1.12	1.02,1.24	.02	38	1.23	1.02,1.48	.03	42	1.28	1.06,1.55	.01	50	1.09	0.99,1.21	.09	5
Cancer type																						
Breast	2	1235/1260	2.07	0.55,7.70	.28	96	2.23	0.53,9.36	.27	96	NA	NA	NA	NA	2.22	0.52,9.42	.28	96				
Bladder	2	1226/1601	1.00	0.89,1.12	.99	0	0.96	0.82,1.11	.57	0	1.13	0.88,1.46	.35	28	1.03	0.79,1.36	.82	0	0.85	0.59,1.24	.40	58
Digestive	4	2475/2906	1.15	1.00,1.32	.05	62	1.16	0.96,1.39	.11	61	1.28	1.06,1.54	< .01	14	1.33	1.10,1.62	< .01	52	1.13	1.00,1.26	.04	52
rs3024270 G>C			C vs G				(GC+CC) vs GG				CC vs (GG+GC)				CC vs GG				GC vs GG			
Total	5	3220/4287	1.05	0.98,1.12	.14	33	1.06	0.96,1.17	.22	0	1.11	0.98,1.26	.09	8	1.11	0.97,1.27	.13	40	1.04	0.94,1.16	.41	0
Cancer type																						
digestive	3	1980/2409	1.12	1.03,1.22	< .01	0	1.13	0.99,1.28	.06	0	1.21	1.04,1.41	.01	0	1.27	1.07,1.51	< .01	0	1.08	0.94,1.24	.28	3

[a] *P*-values were obtained from *Z*-test.

[b] I^2 test for heterogeneity.

CI = confidence interval, HB = hospital-based, NA = not available, OR = odds ratio.

strength of conclusions.[42] Overall, our results provide evidence that rs2107425, rs217727, rs2839698, rs2735971, and rs3024270, but not rs3741219 loci, are related to cancer risk, among which rs217727, rs2839698, and rs3024270 increase and rs2107425, rs2735971 decrease cancer risk, respectively. Our results indicate that the lncRNA H19 rs2839698 G>A polymorphism might be an important risk factor for developing digestive system cancer, which is in accordance with previous meta-analyses.[43,44] In contrast, significant decreased risk of cancer was observed for the H19 rs2107425 C>T polymorphism. In subgroup analyses by ethnicity, we found that people with the mutated genotypes of rs2107425 C>T had a protective effect against cancer development in Caucasian populations, illustrating that the decreased cancer risk may be ethno-specific. As for rs217727 G>A polymorphism, we reached a different conclusion compared with the previous three meta-analyses.[43–45] In 2016, Lu et al conducted a meta-analysis of the association between rs217727 polymorphism and cancer risk and reported that this polymorphism was not associated with overall cancer risk. In addition, Chu et al and Li et al carried out another 2 meta-analyses on rs217727 polymorphism and cancer risk correlation, and their conclusions were similar to those of Lu et al. We, however, found significant correlations with increased cancer risk in the Asian populations and in breast cancer subgroup in the studies, restricted to HWE. The discrepancy between our findings and previous meta-analyses might be due to the inclusion of more studies in our case (eleven published reports, involving 12,638 participants). Since we observed a significantly decreased cancer risk in both overall population and in digestive system cancer group, we suggest that rs2735971 C>T polymorphism might be a protective factor, especially for digestive system cancer. In addition, significantly increased cancer risk correlation was observed in the rs3024270 G>C polymorphism analysis.

Based on the important functional influence of folding structure changes of lncRNAs caused by SNPs, we sought to predict the centroid secondary structural changes of H19 SNPs using RNAfold web server. We found that the centroid secondary structure apparently differs along with the polymorphisms of rs217727 G>A and rs2735971 C>T, suggesting that these SNPs may be involved in the onset and progression of cancer by modulating the specific structural motifs of H19, leading to a specific interplay between the lncRNA secondary structure and their biological functions.[46,47] Despite computational algorithms can give large-scale prediction of lncRNA secondary structures, these methods may have a high false-positive rate.[48,49] The results of prediction may aid future lncRNA investigations, providing guidance for further experimental design and verification of their biological functions. Furthermore, a comprehensive whole-genome investigation of lncRNA secondary structures is still missing for human.[46] Using a lncRNA-binding prediction software, we identified that lncRNA H19 with rs217727 G>A alleles could gain hsa-miR-8071 and hsa-miR-4804–5p binding sites, thereby losing hsa-miR-8072 and hsa-miR-3960 binding elements. It is unclear, how rs217727 polymorphisms can affect the susceptibility to cancer by obtaining and losing miRNAs; therefore, further studies are needed to explore the underlying specific mechanisms. Moreover, we predicted that the rs2839689 G>A polymorphism could create hsa-miR-6894–3p, hsa-miR-4674, hsa-miR-6514-3p, and hsa-miR-378 g binding sites and destroy hsa-miR-24-1-5p, hsa-miR-24-2-5p, hsa-miR-4486, and hsa-miR-566 miRNA binding sites on H19. Interestingly, overexpression of miR-378 g

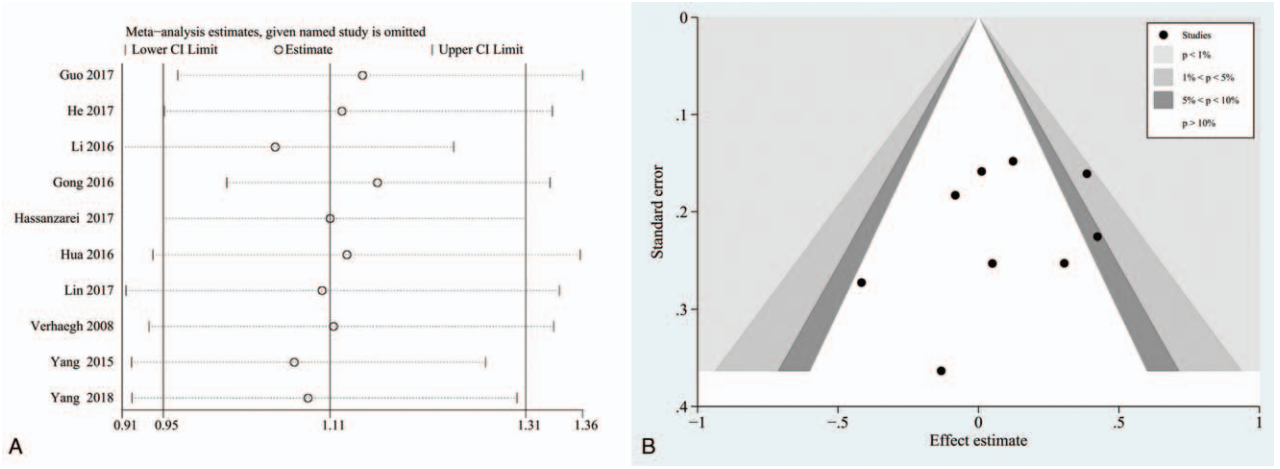

Figure 3. (A) Sensitivity analysis via deleting each study to reflect the influence of the individual dataset to the pooled ORs between H19 rs2839698 G>A polymorphism and cancer susceptibility in homozygous model (AA vs GG). (B) Funnel plot analysis to detect publication bias for the homozygous model (AA vs GG) of H19 rs2839698 G>A polymorphism.

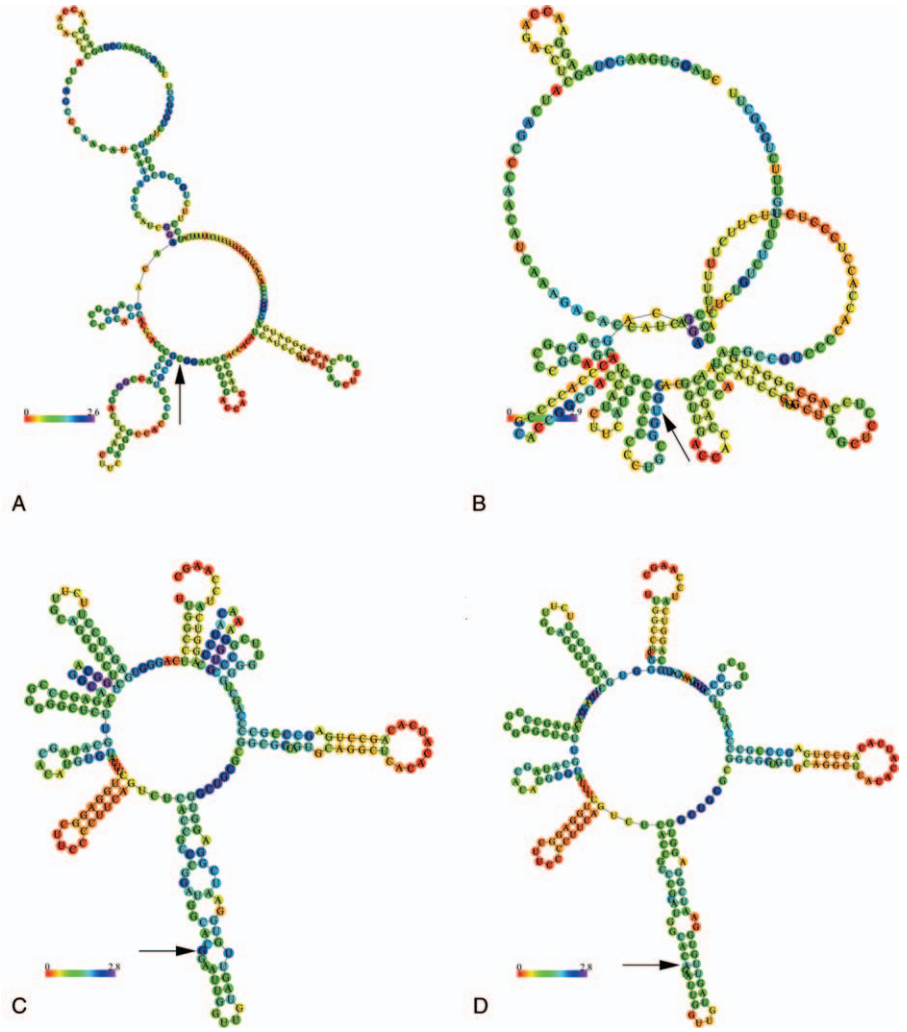

Figure 4. Bioinformatic prediction of H19 polymorphisms on centroid secondary structure. (A) centroid secondary structure of rs217727 C allele; (B) centroid secondary structure of rs217727 T allele; (C) centroid secondary structure of rs2735971 A allele; (D) centroid secondary structure of rs2735971 G allele. Arrows indicate the position of SNP allele.

enhances radiosensitivity, promotes apoptosis, and decreases invasion in nasopharyngeal carcinoma cells.[50] Zhang et al found that the overexpression of miR-24-1-5p facilitates epithelial ovarian tumor cell proliferation by downregulating p21 activated kinase 4 (PAK4) expression, which is 1 of the downstream key targets of miR-24-1-5p.[51] Bing et al. showed that downregulation of miR–566 increases the expression levels of VHL, decreases the expression levels of VEGF, and inhibits the invasive and migratory abilities of glioblastoma.[52] Thus, it is biologically conceivable that the gain and loss of miRNAs functions, owing to the SNPs of H19, may regulate the expression of H19 and thereby influence proliferation, migration and invasion of some cancer cells. However, further experimental functional studies should be performed to prove this hypothesis.

As far as we know, this is the first meta-analysis, particularly focusing on the relationship between the six lncRNA H19 gene polymorphisms and tumor susceptibility. Although eighteen studies involve relatively small sample size of 17, 090 cases and 23, 532 controls, we believe that our findings can help to explain the associations between lncRNA H19 polymorphisms and cancer risk. First, by discarding each study 1-by-1, sensitivity analysis was performed to evaluate the relative stability and credibility of the results. No significant changes were found in the sensitivity analysis, indicating that the results of our research are robust. Second, except for 1 study related to rs217727 polymorphism, the genotype distributions in the controls of 6 selected SNP loci were all consistent with HWE. Third, the symmetry of the funnel plot and the results of Egger test indicated that no apparent publication bias existed in our meta-analysis, except for rs3741219 polymorphism, where, presumably, insufficient number of studies was involved. Furthermore, based on the modified NOS for evaluation of the quality of the included studies, we are confident about the quality of our meta-analysis results. All the above-mentioned characteristics guarantee the reliability of the presented results.

Nevertheless, there are a few potential limitations in our meta-analysis study. First, heterogeneity existed in all six polymorphism loci. The source of heterogeneity may be attributed to the ethnic diversity, genotyping method, cancer type, and source of control,[53] that is why subgroup analyses were performed to explore the sources of heterogeneity. For all the 6 polymorphism loci, heterogeneity was not effectively eliminated by subgroup analysis, indicating that all aforementioned factors should be taken into consideration. Second, cancer is a complex malignant disease that is caused by interactions between transgenation, environmental change, lifestyle, dietary habit, age, and gender. In some of our studies, detailed information such as age, sex, smoking and drinking habits was not provided, which further limited the stratification analyses. Third, in our study, all patients were from Asia or Caucasus, limiting the general use of the results in other populations. Fourth, in this study we only analyses the association between long non-coding RNA H19 polymorphisms and cancer susceptibility in breast and digestive cancer, but for ovarian, bladder and other types of cancer the analyses were limited duo to the number of included studies. Finally, the six lncRNA H19 polymorphisms were analyzed separately, and the effects between gene-gene, gene-environment, and multiple polymorphic loci could not be assessed with the available data. In our meta-analysis, we only analyzed the H19 polymorphisms, while the fundamental underlying mechanisms cannot be explained clearly due to the lack of information.

In conclusion, the present meta-analysis provides evidence that five functional polymorphisms of H19, involving rs2107425, rs217727, rs2839698, rs2735971, and rs3024270 might contribute to genetic susceptibility to the cancer risk, whereas rs3741219 may have no impact. Given the limitations in the current meta-analysis, we should treat the results with caution. Well-designed and large-scale case-control studies should be conducted to confirm the associations of the abovementioned functional polymorphisms in lncRNA H19 and cancer risk in the future.

Acknowledgments

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Author contributions

Wei Li, Xia Jiang, and Zengren Zhao designed the study. Wei Li and Xiaojing Jin performed the study and wrote the paper. Wei Li, Weitao Yan, and Ying Liu assessed the studies included in this review and collected the data. Wei Li and Dongyun Li analyzed the data. Xia Jiang and Zengren Zhao reviewed the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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