Meta-analysis and trial sequential analysis of LncRNA H19 polymorphic variants on susceptibility to cancer

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Abstract

Background: Although myriad researches upon the associations between LncRNA H19 polymorphic variants (rs2839698 G↔A, rs3024270 C↔G, rs2107425 C↔T, rs2735971 A↔G and rs217727 G↔A) and the susceptibility to cancer have been conducted, these results remained contradictory and perplexing. Basing on that, a systematic review and updated meta-analysis was conducted to anticipate a fairly precise assessment about these associations. **Methods:** We retrieved the electronic databases EMBASE, PubMed and Web of Science for valuable academic studies before October 1st, 2019. Ultimately, 24 of which were encompassed after screening, and the available data was extracted and integrated. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) was adopted to evaluate the strength of these associations. For multi-level investigation, subgroup analysis derived from source of controls together with genotypic method was preformed. Eventually, 24 articles altogether embodying 52 studies were included. **Results:** The results illuminated that LncRNA H19 SNPs mentioned above were all irrelevant to cancer susceptibility. Nevertheless, crucial results were found concentrated in population-based control group when subgroup analysis by source of controls were performed in H19 mutation rs2839698 and rs2735971. Meanwhile, in the stratification analysis by genotypic method, apparent cancer risks were discovered by TaqMan method in H19 mutation rs2107425 and rs3024270. Then, trial sequential analysis (TSA) demonstrated that the results about such associations were firm evidence of effect, except rs2735971 polymorphism. **Conclusion:** Therefore, this meta-analysis indicated that LncRNA H19 SNPs were not associated with the susceptibility to human cancer. However, after the stratification analysis, inconsistent results still existed in different genotypic method and source of control. Thus, more high-quality studies on cancer patients of different factors were needed to confirm these findings.

Background

Continuously threatening public health worldwide, malignant tumor has long been the second biggest cause of death in the developed countries. 1,762,450 new cancer cases and 606,880 cancer mortalities are predicted to occur in the USA in 2019[1]. Nevertheless, the pathogeny of malignant tumor still remains vague. Consensus amongst worldwide researchers is that both the environmental and genetic abnormality contribute to the carcinogenesis[2]. The aberration of genetic expression increases the risk of the initiation and progression of cancer[3]. Accumulating studies have been focusing on the repercussions of long non-coding RNA (lncRNA) mutation which has a place in the genetic factors mentioned above[4–7].

H19 is a 2.3 kb lncRNA without the open reading frames, located in chromosome 11p15.5 [8]. The H19 gene, which is maternal imprinted and expressed, plays an irreplaceable role during embryonic phase and decreases in postpartum mature tissues[9]. As we know, LncRNA H19 is considered as a vital factor associated with, cancer susceptibility included, various biological process which impacts the invasion, metastasis, recurrence and poor prognosis of cancer[10]. It might extend the influence upon the development and progression of disease through the regulation of expression on and after transcription of the oncogene and antioncogene[11]. An increasing amount of researches have found the up-regulation of H19 gene in almost overall cancer, such as breast cancer, bladder cancer, gastric cancer, hepatocellular cancer and so on[4–7;12].

Single nucleotide polymorphisms (SNPs), a type of genetic mutation, affect the gene expression and function, accordingly causing carcinogenesis[13]. Previous studies have indicated the associations between the risks of cancer and several SNPs (rs2839698 G↔A, rs3024270 C↔G, rs2107425 C↔T, rs2735971 A↔G and rs217727 G↔A)[14–18]. For instance, Wang et al. conducted a study and found that H19 polymorphism rs217727 might influence the susceptibility to non-small cell lung cancer[19]. However, another study conducted by Lv et al. showed no association between H19 polymorphism rs217727 and overall cancer susceptibility was found[20]. In that case, though considerable researches have been performed, pooled results seem to be conflicting. Herein, this meta-analysis aimed at deriving a more accurate evaluation in all relevant published studies of the associations between the H19 SNPs and overall cancer susceptibility.

Materials And Methods

We comprehensively retrieved the electronic databases EMBASE, PubMed and Web of Science for all relevant articles published before January 1st, 2020, utilizing terms including 'H19 gene', 'polymorphisms' or 'genetic mutation' with 'LncRNA' or 'H19 SNPs', and 'cancer susceptibility' or 'tumor'. Potential eligible studies were collected and integrated by manual work. Additionally, we then removed the duplicate data from different articles.

Meanwhile, the remaining articles were screened by following criteria: (1) Presented original data from case-control or cohort studies; (2) Existing one or more relevant H19 SNPs (rs2839698 G↔A, rs3024270 C↔G, rs2107425 C↔T, rs2735971 A↔G and rs217727 G↔A); (3) Enrolled patients with cancer histopathological diagnosis definitely, and control groups without primary malignancy; (4) Availability of subgroup analysis statistical data of both cases and controls. Correspondingly, the studies enrollment followed these exclusive criteria: (1) Without available data; (2) Without valuable results related to H19; (3) No case-control study.

Data extraction

The available data from articles after screening were extracted and integrated respectively by two investigators (KP Wang and Z Zhu). Upon the appearance of divergence, a third investigator (YQ Wang) would take intervention. All the data collected were integrated in an united form, especially with regard to the following information: First author's name, Publication year, Ethnicity, Source of controls, Genotypic method, The number of cases and controls, The number of H19 polymorphisms carriers and non-carriers respectively as well as The results of the Hardy-Weinberg equilibrium test.

Statistical analysis

In the meta-analysis, the ORs with 95% CIs were used to estimate the strength of the associations between the H19 SNPs and cancer susceptibility, and comparisons of the allele, homozygous, heterozygous, dominant and recessive model were applied. Q-test and I^2 statistic were used to assess heterogeneity

across studies. $I^2 < 50\%$ suggested no obvious heterogeneity, in which case fixed effect model should be selected for calculation; only $I^2 \geq 50\%$ should the random effect model be selected. Generally, several factors, such as experimental scheme, sex, age, ethnicity, genotypic method and so on, could stimulate the heterogeneity. Therefore, subgroup analysis derived from source of controls and method of genotyping was conducted, aiming at investigating the source of heterogeneity. The Hardy-Weinberg equilibrium (HWE) test was adopted in the control groups to evaluate the gene and genotype frequency, and P value exceeded 0.05, guaranteeing a significant equilibrium. In addition, considering the examination of the stability and reliability of the results, sensitive analysis was adopted through consecutively omitting one study per time. Meanwhile, we conducted both Egger's test and Begg's funnel plots in order to verify the publication bias among these studies. Statistical data was analyzed through Stata statistical software (Version 12.0, Stata Corporation, College Station, TX, USA).

Trial sequential analysis

The results of the meta-analysis should relate the total number of randomized participants accounting for statistical diversity to avoid type I errors. Thus, TSA was performed to estimate the required information size. TSA could confirm greater statistical data reliability through modifying the threshold with dispersive data for significance level. We then calculated the required information size and constructed the trial sequential monitoring boundaries (the sloping red line). If the blue line (representing the cumulative Z-curve) crossed the sloping red line or exceeded the vertical red line (representing the information size required), a sufficient information size would be guaranteed and crucial result would be reached. On the contrary, either of the red line not being reached reveals that additional clinical trials were necessary to guarantee the sufficient information size for further verification. The TSA software (TSA, version 0.9, 2011; Copenhagen Trial Unit, Copenhagen, Denmark) was adopted in this study.

Results

Studies characteristics

Primitively, a total of 182 articles were collected under the guidance of the retrieve strategy above for further screening. Then, 24 articles containing 52 studies met the inclusive criteria, ranging from February 2008 to July 2019 as for publish date [15-16;21-33]. The flow pathway was shown in **Figure 1**. [34-40] Distribution of the genotypes in the controls satisfied with HWE. The baseline characteristics of all the studies were extracted and tabulated in **Table 1**. Asians, Caucasians, Africans and Mixed were involved in these studies. We separated these studies into population-based (PB) and hospital-based (HB) groups to help differentiate between various sources of control. Moreover, the studies collected performed eight genotypic methods altogether, for instance, Illumina, Taqman, Sequenom, etc.

Meanwhile, we calculated the pooled ORs and 95% CIs using five genetic model in order to assess the association between lncRNA H19 polymorphisms and cancer susceptibility, results of which were tabulated in **Table 2**. Also, stratification analysis by source of controls along with genotypic method was applied to investigate the heterogeneity of all studies.

rs2839698 G/A and cancer susceptibility

Thirteen studies about lncRNA H19 rs2839698 G/A polymorphism and the susceptibility to cancer consisting 7,351 cases and 10,066 controls met the inclusive criteria. The pooled ORs were 1.08 (95% CI: 0.98-1.19) for allele model, 1.08 (95% CI: 0.96-1.23) for dominant model, 1.06 (95% CI: 0.94-1.20) for homozygote model, 1.15 (95% CI: 0.94-1.41) for heterozygote model and 1.12 (95% CI: 0.96-1.31) for recessive model (**Figure 2**). Despite of no positive results, significant association between rs2839698 G/A and cancer susceptibility in population-based controls (allele model: OR=1.17, 95% CI: 1.04-1.31; homozygote model: OR=1.41, 95% CI: 1.04-1.91; recessive model: OR= 1.46, 95% CI: 1.13-1.89) was observed in the stratification analysis by source of control. In addition, no significant results were detected in the subgroup analysis as to the methods of genotyping.

rs217727 G/A and cancer susceptibility

Herein, 15 Studies focusing on rs217727 G/A polymorphism and cancer susceptibility included 8,164 cases and 10,963 controls. No significant association was indicated through the pooled risk estimation under allele model (OR=1.03, 95% CI=0.94-1.13), dominant model (OR=1.06, 95% CI=0.93-1.22), heterozygous model (OR=1.07, 95% CI=0.92-1.23), homozygous model (OR=1.02, 95% CI=0.85-1.21) and recessive model (OR=0.99, 95% CI=0.84-1.16) (**Figure 3**). Besides, no positive results were observed in either of the subgroup analysis by source of control and genotypic method.

rs2107425 C/T and cancer susceptibility

A total of 11 studies embodying 17,628 controls and 12,292 cases were investigated to lncRNA H19 polymorphic variants rs2107425 C/T and the susceptibility to cancer. Analogously, no significant association between rs2107425 C/T polymorphism and cancer risk was shown in the meta-analysis according to the pooled ORs of these studies under allele model (OR=0.96, 95% CI=0.89-1.04), dominant model (OR=0.95, 95% CI=0.85-1.06), heterozygous model (OR=0.95, 95% CI=0.84-1.07), homozygous model (OR=0.97, 95% CI=0.83-1.13) and recessive model (OR=0.98, 95% CI=0.87-1.12) (**Figure 4**). Nevertheless, as to the stratification analysis of genotypic method, the result was significant only in TaqMan (allele model: OR=0.86, 95% CI=0.80-0.94), while no significant results was detected in subgroup of source of control.

rs2735971 A/G and cancer susceptibility

The present meta-analysis enrolled 4,393 controls and 3,522 cases from a sum of six studies on rs2735971 A/G polymorphism and cancer susceptibility. No significant association was observed among these studies (allele model (OR=0.91, 95% CI=0.75-1.11), dominant model (OR=0.72, 95% CI=0.44-1.17), heterozygous model (OR=0.68, 95% CI=0.41-1.13), homozygous model (OR=0.76, 95% CI=0.45-1.29) and recessive model (OR=0.99, 95% CI=0.89-1.11)).

(Figure 5). Additionally, the results of stratified analysis by genotypic method were not positive. By contrast, in subgroup analysis by source of control, feebly positive results were shown in PB control with (dominant model: OR=0.85, 95% CI=0.71-1.00; heterozygous model: OR=0.83, 95% CI=0.70-0.99).

rs3024270 C↯G and cancer susceptibility

No significant association existed between rs3024270 mutation and cancer susceptibility as shown by the pooled risks of 8 relevant studies consisting 4,211 cases and 6,014 controls under allele model (OR=1.03, 95% CI=0.98-1.10), dominant model (OR=1.07, 95% CI=0.97-1.18), heterozygous model (OR=1.05, 95% CI=0.95-1.17), homozygous model (OR=1.09, 95% CI=0.97-1.23) and recessive model (OR=1.03, 95% CI=0.94-1.13) (Figure 6). However, stratification analysis by source of control indicated significant association with cancer susceptibility in the PB control group (homozygous model: OR=1.28, 95% CI=1.01-1.61). Additionally, the results of analysis stratified by genotypic method were more significant while using TaqMan than non-TaqMan methods (allele model: OR=1.08, 95% CI=1.01-1.16, dominant model: OR=1.12, 95% CI=1.00-1.26 and homozygous model: OR=1.21, 95% CI=1.05-1.39).

Sensitivity analysis

We performed sensitivity analysis by excluding single eligible study sequentially to detect individual study's influence on the pooled results. According to the results, no single study was found affect the pooled OR in the allele model, suggesting a statistically robust results (Figure 7).

Publication bias

Both Egger's test and Begg's funnel plot were utilized in the selected literature. With the symmetrical shapes of funnel plots shown in Figure 8, the absence of publication bias could be testified in the allele model (rs2839698: $P=0.222$, rs217727: $P=0.882$, rs2107425: $P=0.421$, rs2735971: $P=0.851$ and rs3024270: $P=0.322$).

Trial sequential analysis results

In this meta-analysis, Figure 9 showed that the information sizes of all the H19 mutations investigated were sufficient except rs2735971 A↯G polymorphism, indicating that the results about the associations between LncRNA H19 polymorphic variants (rs2839698 G↯A, rs3024270 C↯G, rs2107425 C↯T and rs217727 G↯A) and the susceptibility to cancer were firm evidence of effect, and the further verification is necessary for the relationship of rs2735971 A↯G mutation and cancer risk.

Discussion

An growing amount of researches have been focusing on the mutation of H19 when it comes to the genesis and development of various cancer[41]. As a long non-coding RNA, H19 lacks the open reading frame to translate protein whose end product is RNA sequence and can participate in downstream RNA regulatory[21;42]. LncRNA H19 is an imprinted gene the aberrant expression of which is associated with cancer susceptibility[22]. In this meta-analysis, SNPs (rs2839698 G↯A, rs3024270 C↯G, rs2107425 C↯T, rs2735971 A↯G and rs217727 G↯A) were contained to explore the relationship between these polymorphisms and the risk of cancer.

Previously, several meta-analysis on aberration of H19 have been conducted thanks to the identification of numerous lncRNAs[23-24]. Though the results were contrary to many studies, a meta-analysis conducted by Lv et al. revealed that rs217727 were uncorrelated to overall cancer risk[20]. It might account for the lack of the interactive microRNAs (miRNAs) which could influence the regulation and modification of lncRNAs SNPs directly[20;43]. In that case, the site where structural gene alteration (such as mutation, deletion, insertion etc) caused by the SNPs might be at variance with the binding position of miRNAs that regulate lncRNA expression, thus indicating no significant association with overall cancer risk. Also, another meta-analysis conducted by Li et al. inspired us on the possible reason[44]. The various cancer location and patient ethnicity probably account for the discrepancies amongst these studies. In these studies, a small sample size and controversial results caused by the former factor might make these analysis relatively unreliable. Herein, we conducted this meta-analysis with the largest sample capacity and the most up-to-date studies and data, comprehensively analyzing all literatures to study such association. According to quantitative synthesis results, all the mutation mentioned above were found no significant association.

While stratified by source of control, significant association was found in the PB control group between rs2839698, rs2735971 and rs3024270 polymorphisms and the susceptibility to cancer, whereas no significant results were detected in their HB control group. Lack of the representativeness might account for the phenomena. Moreover, referring to subgroup analysis of genotypic method, significant association was also detected between the risk of cancer and rs2107425, rs3024270 polymorphisms adopting TaqMan method for genotyping, whereas similar results were not found while using other genotypic methods. The possible reason might be that different genotypic methods lead to different statistical results owing to their relative merits. The merits of TaqMan are the lower probability of PCR pollution due to that the reaction happens in PCR process, avoiding separation and elution[45].

TSA, as an statistical tool, is similar to interim analysis in a single trial, where trial monitoring boundaries are drawn for each outcome whether to continue additional trials to assess for evidence while a P value is small enough to show the projected effect or for futility[46]. The association shown in the results of this meta-analysis could be unreliable accounting for limited data. Therefore, TSA was adopted in order to diminish the probability of type I error and verify whether the evidence of our results was adequate or not. The results about the associations between LncRNA H19 polymorphic variants (rs2839698, rs217727, rs2107425 and rs3024270) and the susceptibility to cancer were firm evidence of effect. However, the cumulative Z-curve of H19 rs2735971 polymorphism neither crossed the trial sequential monitoring boundary nor exceeded the required information size, indicating that false positive results might be eliminated in advance due to repeated significance testing and random errors in meta-analysis[47]. In order to obtain results with firm evidence, further verification is necessary.

Inevitably, several additional limitations should be warranted in this meta-analysis. (1). As a multifactorial disease, overall cancers are influenced by genetic combined with environmental factors. Focusing on single gene region, this meta-analysis ignored the complex interaction between various factors, in which case the association was unilateral; (2). The scale of studies collected was fairly narrow, referring to the subgroup analysis. Also, the amount of these studies needs to be expanded. Subgroups with less than three studies were retained, thus might causing the potential false associations; (3). The ethnicities of studies were concentrated on Asian , which means the results might not applicable for all population. Hence, to ensure reliability of our meta-analysis, attention must be paid to the influence of various factors in the future studies of more large-sample, multi-center and high-quality researches.

Conclusion

To conclude, the results of this meta-analysis revealed that five H19 SNPs (rs2839698 G→A, rs3024270 C→G, rs2107425 C→T, rs2735971 A→G and rs217727 G→A) had no significant association with the overall cancer susceptibility, thereby suggesting that H19 might not have clinical significance in cancer diagnosis and treatment. However, after the stratification analysis, inconsistent results still existed in different genotypic method and source of control. Thus, more high-quality studies on cancer patients of different factors were needed to confirm these findings.

Abbreviations

TSA, Trial sequential analysis;

LncRNA, Long non-coding RNA;

SNP, Single nucleotide polymorphisms;

miRNA, microRNAs;

HWE, Hardy-Weinberg equilibrium;

ORs, Odds ratios;

CI, Confidence intervals.

Declarations

Ethics approval and consent to participate

None declared.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and material

All data on which the conclusions rely are either deposited in publicly available repositories or presented in the main papers or additional supporting files.

Competing interests

We declare that we have no conflict of interest.

Authors' contributions

Protocol/project development: CQ Tu, KP Wang and Z Zhu

Data collection or management: Z Zhu, JB Gu and KP Wang

Data analysis: YQ Wang, DY Zong and P Xue

Manuscript writing/editing: Z Zhu, DY Lu and KP Wang.

All authors have read and approved the manuscript.

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Tables

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

Year	Surname	Ethnicity	SOC	Genotyping	Type	Cases	Controls	Gene polymorphism	HWE
2019	Wang	Asian	HB	TaqMan	LC	564	1536	rs2839698 rs217727	Y
2019	Li	Asian	HB	TaqMan	BC	200	200	rs217727 rs2735971 rs3024270	Y
2019	Mohammad	Asian	HB	4P-ARMSPCR	BCa	111	130	rs2839698 rs217727	Y
2019	Wu	Asian	HB	TaqMan	HCC	359	1190	rs2839698 rs217727 rs2107425 rs3024270	Y
2019	Yang	Asian	HB	PCR	BC	431	431	rs2839698 rs217727 rs2107425 rs3024270	Y
2018	Yang	Asian	HB	KASP	HCC	472	472	rs2839698 rs2735971 rs3024270	Y
2018	Cui	Asian	HB	TaqMan	BCa	1491	1677	rs2839698 rs217727	Y
2018	Yin	Asian	PB	Illumina	LC	556	395	rs217727 rs2107425	Y
2018	Abdollahzadeh	Asian	HB	PCR-RFLP	BCa	150	100	rs217727	Y
2017	Guo	Asian	HB	Illumina	OSCC	362	741	rs2839698 rs217727 rs2735971 rs3024270	Y
2017	He	Asian	HB	TaqMan	OSC	193	383	rs2839698 rs217727 rs2735971 rs3024270	Y
2017	Hu	Asian	HB	TaqMan	PC	416	416	rs217727	Y
2016	Li	Asian	PB	TaqMan	CRC	1147	1203	rs2839698 rs217727 rs2735971 rs3024270	Y
2016	Hua	Asian	HB	TaqMan	BC	1049	1397	rs2839698 rs217727 rs2735971 rs3024270	Y
2016	Gong	Asian	HB	TaqMan	LC	496	206	rs2839698 rs2107425	Y
2016	Xia	Asian	PB	CRS-RFLP	BCa	464	467	rs217727	Y
2015	Yang	Asian	HB	TaqMan	GC	500	500	rs2839698 rs217727	Y
2014	Barnholtz-Sloan 11	Caucasian	PB	Illumina	BCa	1225	1118	rs2107425	Y
2014	Barnholtz Sloan 12	Africa	PB	Illumina	BCa	737	658	rs2107425	Y
2012	Butt	Caucasian	PB	Sequenom	BCa	678	1355	rs2107425	Y
2009	Song	Caucasian	PB	TaqMan Sequenom MassArray	OC	5366	8538	rs2107425	Y
2009	Quaye	Caucasian	PB	TaqMan	OC	1460	2463	rs2107425	Y
2008	Verhaegh	Caucasian	PB	PCR-RFLP	BC	177	204	rs2839698 rs217727 rs2107425	Y
2008	Bhatti	Mixed	PB	Sequenom	BCa	824	1073	rs2107425	Y

Abbreviation: SOC: source of control; HB: hospital-based; HWE: Hardy-Weinberg equilibrium;

BC: Bladder cancer; BCa: Breast cancer; LC: Lung cancer; HCC: Hepatocellular cancer; OSCC: Oral squamous cell carcinoma; OSC: Osteosarcoma; PC: Pancreatic cancer; CRC: Colorectal cancer; GC: Gastric cancer; OC: Ovarian cancer;

Figures

Table 2. Meta-analysis results for the included studies of the association between LncRNA H19 polymorphisms and risk of cancer.

Variables No. of studies		Allele model			Dominant model			Heterozygous model			Homozygous model		
		OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	
		A vs G			(GA+AA) vs GG			GA vs GG			AA vs GG		
39698 G/A													
All	13	1.08(0.98,1.19)	<0.001	72.6	1.08 (0.96,1.23)	<0.001	71.3	1.06 (0.94,1.20)	0.001	66.8	1.15 (0.94,1.41)	<0.001	
Source of control													
PB	2	1.17 (1.04,1.31)	0.347	<0.1	1.02 (0.68,1.54)	0.076	68.2	0.91 (0.53,1.55)	0.032	78.2	1.41 (1.04,1.91)	0.290	
HB	11	1.07 (0.96,1.20)	<0.001	74.5	1.09 (0.95,1.26)	<0.001	73.2	1.08 (0.95,1.24)	0.001	67.0	1.12 (0.89,1.41)	<0.001	
Method of genotype													
TaqMan	8	1.05 (0.96,1.14)	0.024	56.5	1.07 (0.96,1.18)	0.052	49.9	1.06 (0.96,1.17)	0.108	40.6	1.08 (0.89,1.32)	0.038	
non-TaqMan	5	1.19 (0.90,1.56)	<0.001	85.4	1.18 (0.80,1.76)	<0.001	85.7	1.09 (0.75,1.60)	<0.001	82.8	1.41 (0.84,2.38)	<0.001	
		A vs G			(GA+AA) vs GG			GA vs GG			AA vs GG		
7727 G/A													
All	15	1.03 (0.94,1.13)	<0.001	70.9	1.06 (0.93,1.22)	<0.001	74.0	1.07 (0.92,1.23)	<0.001	74.1	1.02 (0.85,1.21)	0.002	
Source of control													
PB	4	0.97 (0.83,1.13)	0.051	61.4	0.90 (0.72,1.11)	0.048	62.1	0.85 (0.66,1.11)	0.014	71.6	0.97 (0.75,1.26)	0.154	
HB	11	1.06 (0.94,1.19)	<0.001	73.1	1.14 (0.97,1.35)	<0.001	73.4	1.16 (0.99,1.37)	<0.001	69.5	1.03 (0.82,1.30)	0.002	
Method of genotype													
TaqMan	8	1.04 (0.94,1.15)	0.005	65.5	1.13 (0.96,1.33)	<0.001	74.0	1.15 (0.97,1.37)	0.056	74.8	1.00 (0.81,1.23)	0.010	
non-TaqMan	7	0.99 (0.80,1.21)	<0.001	78.1	0.96 (0.73,1.27)	<0.001	77.6	0.94 (0.70,1.24)	<0.001	76.5	1.02 (0.72,1.44)	0.020	
		T vs C			(CT+TT) vs CC			CT vs CC			TT vs CC		
77425 C/T													
All	10	0.96 (0.89,1.04)	0.001	68.5	0.95 (0.85,1.06)	<0.001	71.5	0.95 (0.84,1.07)	<0.001	71.6	0.97 (0.83,1.13)	0.010	
Source of control													
PB	7	0.96 (0.88,1.06)	<0.001	75.8	0.92 (0.80,1.06)	<0.001	77.8	0.90 (0.78,1.03)	<0.001	75.5	1.01 (0.85,1.19)	0.016	
HB	3	0.96 (0.82,1.13)	0.154	46.6	1.04 (0.88,1.23)	0.360	2.1	1.12 (0.94,1.32)	0.602	<0.1	0.85 (0.59,1.22)	0.114	
Method of genotype													
TaqMan	3	0.86(0.80,0.94)	0.396	<0.1	0.86 (0.71,1.05)	0.098	57.0	0.90 (0.68,1.21)	0.013	76.9	0.81 (0.62,1.04)	0.206	
non-TaqMan	7	1.00 (0.91,1.10)	0.004	68.9	0.99 (0.86,1.13)	0.002	70.6	0.97 (0.85,1.11)	0.006	66.9	1.04 (0.87,1.24)	0.028	
		G vs A			(AG+GG) vs AA			AG vs AA			GG vs AA		
35971 A/G													
All	6	0.91 (0.75,1.11)	<0.001	81.9	0.72 (0.44,1.17)	<0.001	86.8	0.68 (0.41,1.13)	<0.001	86.3	0.76 (0.45,1.29)	<0.001	
Source of control													
PB	1	0.89 (0.77,1.03)	-	-	0.85 (0.71,1.00)	-	-	0.83 (0.70,0.99)	-	-	0.99 (0.63,1.55)	-	
HB	5	0.92 (0.72,1.19)	<0.001	85.5	0.69 (0.35,1.34)	<0.001	85.0	0.65 (0.33,1.29)	<0.001	84.4	0.71 (0.38,1.34)	<0.001	
Method of genotype													
TaqMan	4	0.96 (0.87,1.05)	0.503	<0.1	0.86 (0.66,1.12)	0.229	30.6	0.84 (0.63,1.12)	0.205	34.5	0.92 (0.66,1.30)	0.257	
non-TaqMan	2	0.82 (0.45,1.50)	<0.001	93.9	0.55 (0.16,1.86)	0.004	87.8	0.50 (0.15,1.67)	0.006	86.6	0.58 (0.18,1.90)	0.006	
		G vs C			(CG+GG) vs CC			CG vs CC			GG vs CC		
24270 C/G													
All	8	1.03 (0.98,1.10)	0.237	24.1	1.07 (0.97,1.18)	0.630	<0.1	1.05 (0.95,1.17)	0.811	<0.1	1.09 (0.97,1.23)	0.218	
Source of control													
PB	1	1.11 (0.99,1.25)	-	-	1.06 (0.90,1.26)	-	-	0.99 (0.82,1.18)	-	-	1.28 (1.01,1.61)	-	
HB	7	1.01 (0.95,1.08)	0.293	17.9	1.07 (0.95,1.20)	0.513	<0.1	1.09 (0.96,1.23)	0.809	<0.1	1.04 (0.90,1.19)	0.297	

Method of genotype												
TaqMan	5	1.08 (1.01,1.16)	0.873	<0.1	1.12 (1.00,1.26)	0.788	<0.1	1.08 (0.96,1.22)	0.622	<0.1	1.21 (1.05,1.39)	0.851
non-TaqMan	3	0.93 (0.84,1.03)	0.309	14.9	0.95 (0.79,1.14)	0.532	<0.1	0.99 (0.82,1.20)	0.763	<0.1	0.88 (0.71,1.08)	0.353

Figure 1

The flow diagram of literature retrieval and screening process.

Figure 2

Forest plot of the association between H19 polymorphism rs2839698 G>A and cancer susceptibility under five genetic model. A: allele; B: dominant; C: heterozygote; D: homozygote; E: recessive.

Figure 3

Forest plot of the association between H19 polymorphism rs2839698 G>A and cancer susceptibility under five genetic model. A: allele; B: dominant; C: heterozygote; D: homozygote; E: recessive.

Forest plot of the association between H19 polymorphism rs217727 G↔A and cancer susceptibility under five genetic model. A: allele; B: dominant; C: heterozygote; D: homozygote; E: recessive.

Figure 4

Forest plot of the association between H19 polymorphism rs2107425 C↔T and cancer susceptibility under five genetic model. A: allele; B: dominant; C: heterozygote; D: homozygote; E: recessive.

Figure 5

Forest plot of the association between H19 polymorphism rs2735971 A↔G and cancer susceptibility under five genetic model. A: allele; B: dominant; C: heterozygote; D: homozygote; E: recessive.

Figure 6

Forest plot of the association between H19 polymorphism rs3024270 C↔G and cancer susceptibility under five genetic model. A: allele; B: dominant; C: heterozygote; D: homozygote; E: recessive.

Figure 7

Sensitivity analysis under the allele model. A: rs2839698; B: rs217727; C: rs2107425; D: rs2735971 ; E: rs3024270.

Figure 8

Begg's funnel plot of publication bias test in the allele model. A: rs2839698; B: rs217727; C: rs2107425; D: rs2735971 ; E: rs3024270.

Figure 9

TSA of the association between H19 polymorphisms and the susceptibility to cancer. The calculation of the required information size was based on a 2-sided $\alpha = 5\%$, $\beta = 15\%$ (power 85%), and a relative risk reduction of 20%. A: rs2839698; B: rs217727; C: rs2107425; D: rs2735971 ; E: rs3024270.