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Original Article

Clinical significance of *H19* as a prognostic factor in human cancer: a systematic review and meta-analysis

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Abstract: Background: LncRNA *H19* (*H19*) is known to play a crucial role in tumor development, progression, and prognosis. Methods: A comprehensive meta-analysis was performed by searching PubMed, Medline and EMBASE online databases to retrieve studies relevant to the expression of *H19* and its prognostic value in cancer patients. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for survival were calculated as the effect size to quantify the prognostic value of *H19* in human cancers. Results: Twelve studies with a total of 4500 patients were included in this meta-analysis. Analysis results showed that high expression of *H19* in cancer patients was a negative predictor for overall survival (OS) with a pooled HR of 1.167 (95% CI: 1.055-1.291, *P* = 0.003). No significant association was found between *H19* expression and cancer patients' disease-free survival (DFS) (HR = 1.092, 95% CI: 0.866-1.377, *P* = 0.459). Subgroup analysis results showed that country, method of measuring *H19* expression, publication quality, and statistical analysis method did not affect the predictive value of *H19* in cancer prognosis. Heterogeneity existed among the studies but we failed to identify the source of the heterogeneity. Sensitivity analysis indicated that the results of this meta-analysis were reliable. Begg's and Egger's test found the publication bias between *H19* and OS in cancer, but the results of trim and fill procedure were similar with the general results. Conclusion: High expression of *H19* may be a predictor of poor prognosis in patients with cancer.

Keywords: lncRNA, *H19*, cancer, prognosis, meta-analysis

Introduction

The global burden of cancer is increasing. The American Cancer Society estimated that 1,658,370 new cancer cases and 589,430 cancer deaths occurred in the United States in 2015 [1]. Cancer is the second leading cause of death and expected to surpass heart disease in the near future in the US [1]. A variety of factors contribute to the development of tumors, including external environmental factors, genetic factors, the steady-state of the internal environment, and indirect factors such as age and obesity [2]. A recent study found that a large number of genes in colorectal cancer cells were expressed abnormally and this was mainly caused by changes in the transcriptional regulation of these genes [3].

Long non-coding RNAs (lncRNAs) are RNAs that are longer than 200 nt with no translated protein products, thus executing their biological functions directly as RNA [4]. Recently, a growing body of studies has shown that lncRNAs play important roles in cell growth and differentiation, and affect the growth, development, and metastasis of tumors [5-7]. Furthermore, several studies suggested that lncRNAs may be associated with the prognosis of cancer patients [8, 9]. For example, the average overall survival and progression-free survival time was shorter in postoperative breast cancer patients with high expression of the lncRNA colon cancer associated transcript 1 (*CCAT1*) than in patients with low expression [10]; and high expression of prostate cancer-associated ncRNA transcript 1 (*PACT-1*) in esophageal squamous cell carcinoma indicated poor prognosis [11]. LncRNAs were expected to become biomarkers for cancer diagnosis and prognosis [12].

The *H19* gene was first discovered in 1991 [13]. Same as insulin-like growth factor 2 (*Igf2*), it

belongs to the category of genetically imprinted genes. *H19* is maternally expressed and is located on the distal portion of mouse chromosome 7 and the chromosome 11p15.5 region in the human genome. The human *H19* gene is 2.3 kb long and its mRNA has 35 open reading frames but no corresponding protein product [14, 15]. The *H19* gene is highly expressed during embryonic development. However, its expression is reduced after birth, with only low level of *H19* expression found in cardiac and skeletal muscles [16, 17]. Previous studies have shown that *H19* acts as a tumor suppressor in Wilms' tumor [18, 19], while it has also been reported to be upregulated in many types of cancers, such as colorectal cancer [20] and ovarian cancer [21]. These findings suggest that *H19* could be a biomarker for cancer pathogenesis and progression [22]. In recent years, research has mainly focused on the mechanism and the prognostic value of *H19* in different types of cancers. For instance, *H19* can accelerate breast cancer cell cycle progression and promote cell proliferation via activation of E2F1, which plays a key role in regulating a cell's G1/S transition [23]. Zhang *et al* [24] found that high expression of *H19* positively correlated with tumor size and advanced TNM stage in non-small-cell lung cancer (NSCLC), and *H19* expression could serve as a prognosis factor in NSCLC. Elevated *H19* expression was also found to promote gastric cancer cell proliferation, migration, invasion, and metastasis [25]. A high level of *H19* in breast cancer could enhance the aggressive phenotype and increase tumor growth and metastasis [26]. In addition, a recent study shows that high expression of *H19* may be a poor prognosis factor in hepatocellular carcinoma (HCC) [27].

Although a number of studies have been done to evaluate the association between *H19* gene expression and cancer patient survival, their results are not always consistent, probably because the sample sizes in many of these studies were small, or the research conditions were limited. We conducted a meta-analysis to comprehensively assess the clinical value of *H19* as a prognostic factor in human cancers.

Materials and methods

Search strategy

This systematic review and meta-analysis were conducted by systematically searching the following electronic databases, PubMed, Medline and EMBASE. The language of literature was limited to English. Our core search consisted of the terms "long non-coding RNA or lncRNA", "H19", "cancer, tumor, carcinoma, neoplasm, adenomas, or adenocarcinomas", and "prognosis or prognostic". We collected publications on *H19* and prognosis of cancer patients in accordance with strict inclusion and exclusion criteria. The literature search was for articles published until January 2016.

Inclusion and exclusion criteria

In order to ensure the accuracy and reliability of our meta-analysis, the publications selected from the three databases had to meet the following criteria: (1) studies were published before or in January 2016 on *H19* expression and prognosis in cancer patients; (2) studies should clearly clarify the type of tumor; (3) the sample size and the source of samples should be included in the studies; (4) the studies should contain information about either overall survival (OS) or disease-free survival (DFS) and other survival prognostic indicators with HR and 95% CI, or HR and 95% CI can be obtained through data transformation; (5) if the same study population had been published more than once, the most complete publication was selected. The exclusion criteria were as follows: (1) literature review, case reports, unpublished academic papers, letters, and conference abstracts; (2) studies only involving animals or cell lines; (3) studies in which the evaluation of prognosis was absent; (4) studies with incomplete original data; (5) studies that did not provide HR or 95% CI, or the provided information cannot be converted into HR and 95% CI.

Data extraction and quality assessment

We created an information excerpt database using Microsoft Excel to extract and filter literature information. Data were extracted independently and cross-checked by two investigators. Disagreements were resolved via discussion and consensus. A third investigator made a final decision when the first two could not reach an agreement. The following data were extracted for this meta-analysis: first author's name; year of publication; country in which the participants were enrolled; tumor type; total sample size; numbers of men and women; TNM stage; expression of *H19*; end-points; follow-up period; statistical methods; experimental detection

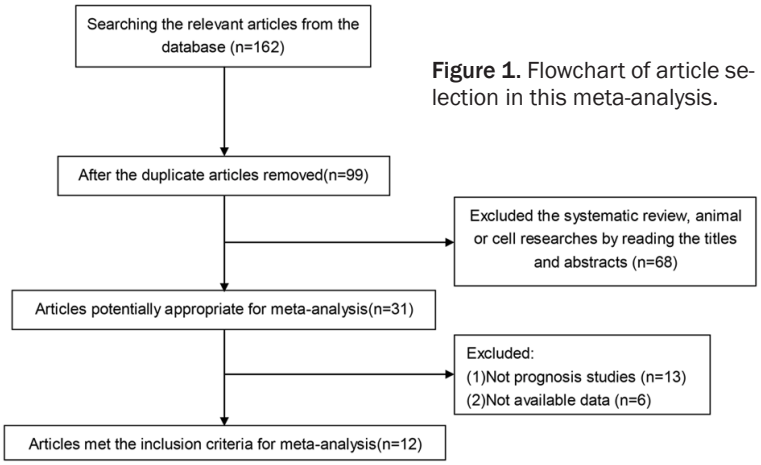

Figure 1. Flowchart of article selection in this meta-analysis.

method; HRs of *H19* and cancer patients for OS, DFS, recurrence-free survival (RFS) and metastasis-free survival (MFS), as well as corresponding 95% CIs; and *P* value.

There were three methods to obtain the HRs and 95% CIs from eligible studies. The first was to directly obtain HRs and 95% CIs from the studies. The second method was used when the studies only contained the *P* value and the number of events. HRs could be calculated with HR = [P0/(1-P0)]/[P1/(1-P1)], where P0 represents the survival rate in *H19* low expression group, and P1 represents the survival rate in *H19* high expression group; and 95% CIs could be obtained with the following equations: SE = var (HR)/√n, 95% CI = exp (lnHR ± 1.96 × SE) [28]. The third method was used when the studies only provided survival curves but not other data. Kaplan-Meier survival curves were used to extract survival data by using the Engauge Digitizer 4.1 software [29], and then HRs and 95% CIs were obtained with the method designed to calculate lnHR and SelnHR by Tierney [28]. This method has been widely used in meta-analysis for survival endpoints [30, 31].

This meta-analysis focused on the association between lncRNA and tumor prognosis, so Steels' evaluation criteria on biological indicators of prognosis were adopted for quality assessment [32]. The assessment included 22 items in the four categories of scientific design, laboratory methodology, generalizability, and result analysis. The highest score of each category was 10 points and the highest total score was 40 points. When an item was not applicable in the quality assessment, the scores were not included in the calculation of the total score. The final scores were expressed as percentages; a higher score indicated a better publication quality. 80% was considered as the threshold of high quality, and a higher percentage represents a publication of better quality.

Statistical analysis

HRs with 95% CIs were used as effective indexes to estimate the relationship between *H19* and tumor clinical prognosis. When selected studies contained the results of both univariate and multivariate analyses, the multivariate analysis results were extracted. The Cochrane Q statistic and I^2 statistic were used to test the heterogeneity among studies, with the former being a qualitative analysis and the latter a quantitative analysis. $I^2 \leq 25\%$ represented a low degree of heterogeneity, $25\% < I^2 \leq 50\%$ a moderate heterogeneity, and $I^2 > 50\%$ a high degree of heterogeneity [33]. A *P* value > 0.1 in combination with $I^2 \leq 50\%$ indicated there was no statistically significant heterogeneity and the fixed-effects model was adopted to calculate the pooled HRs. Otherwise the random-effects model was used.

Subgroup analysis was preformed to identify the potential causes of heterogeneity if it was observed. Subgroup analysis was conducted according to the clinicopathological parameter, residence region, publication quality score and statistical analysis method used by the studies. Sensitivity analysis was preformed to evaluate the stability of results by sequential omission of individual studies. Moreover, funnel plots and Begg's and Egger's tests were used to assess the publication bias, a *P* value ≤ 0.10 was considered statistically significant [34, 35]. We also preformed the nonparametric "trim and fill" procedure to further assess the possible effect of publication bias in our meta-analysis [36]. The possibility of hypothetical "missing" studies was considered exist, the "trim and fill" method was used to impute their HRs, and recalculate a pooled HR that incorporates the hypothetical missing studies as though they actually existed. We performed the meta-analy-

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

First author	Year	Cancer type	Region	No. of cases	Sex (M/F)	TNM Stage	*p* value	Endpoints	Follow-up period	Analysis	Method	Quality score (%)
Li H	2104	Gastric cancer	China	74	54/20	I-IV	0.017	OS	27 months (median)	Univariate	RT-PCR	82.5
Zhang L	2013	Hepatocellular carcinoma (HCC)	China	113	89/24	I-IV	0.008	DFS	21 months (median)	Univariate	RT-PCR	77.5
Couch	2009	Pancreatic Cancer	USA	1143	668/475	NA	NA	OS	271 day	Univariate	NA	62.5
Zhang EB	2014	Gastric cancer	China	80	47/33	I-IV	< 0.001	OS	NA	Univariate and Multivariate	RT-PCR	87.5
Zhang EB	2015	Non-small-cell lung cancer	China	77	46/24	I-IV	< 0.001	OS	NA	Univariate and Multivariate	RT-PCR	87.5
Wang L	2015	Clear cell renal carcinoma (ccRCC)	China	92	57/35	I-IV	< 0.05	OS	From 2007-2010 until September 2013	Univariate and Multivariate	RT-PCR	87.5
Ariel	2000	Bladder carcinoma	Israel	61	49/12	NA	0.03	DFS	NA	Univariate	ISH	75
Iizuka	2004	Hepatocellular carcinoma (HCC)	Japan	59	43/16	I, II, III	NA	RFS	Over 3 years	Univariate	RT-PCR	75
Chen B	2013	Lung cancer	USA	1404	NA	NA	NA	OS	NA	Univariate	RT-PCR	75
Riaz	2012	Breast cancer	Netherlands	1029	NA	NA	NA	MFS	106 months (median)	Univariate and Multivariate	RT-PCR	75
Yang ZG	2015	Hepatocellular carcinoma (HCC)	China	240	199/41	I-IV	< 0.001	OS, DFS	Every 3 months until December 31, 2010	Univariate and Multivariate	NA	77.5
Chen JS	2016	Gastric cancer	China	128	79/59	I-IV	< 0.001	OS, DFS	36 months (median)	Univariate and Multivariate	RT-PCR	90

NA, not available; OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; MFS, metastasis-free survival; HR, hazard ratio; CI, confidence interval; ISH, in situ hybridization; RT-PCR, reverse transcription polymerase chain reaction.

Table 2. Meta-analysis results

Variables	No. of studies	Pooled Hazard Ratio		Model of meta-analysis	Heterogeneity test		Publication bias	
		HR (95% CI)	p_Z		I^2 (%)	p_H	Begg's *P*	Egger's *P*
OS	8	1.167 (1.055-1.291)	0.003	Random	79.90%	< 0.001	0.063	0.075
Region								
China	6	1.176 (1.045-1.323)	0.007	Random	78.80%	< 0.001	0.060	0.055
USA	2	1.136 (0.833-1.547)	0.420	Random	90.60%	0.001	1.000	-
Type of cancer								
Gastric cancer	3	1.388 (1.015-1.900)	0.040	Random	65.90%	0.053	1.000	0.224
Non-small cell lung	2	1.189 (0.977-1.448)	0.084	Random	87.50%	0.005	1.000	-
Method								
RT-PCR	6	1.210 (1.039-1.409)	0.014	Random	78.90%	< 0.001	0.133	0.128
Other	2	1.160 (0.899-1.497)	0.254	Random	91.10%	0.475	1.000	-
Quality score (%)								
< 80	3	1.093 (0.925-1.292)	0.295	Random	85.00%	0.001	0.296	0.689
≥ 80	5	1.340 (1.096-1.640)	0.004	Random	80.40%	< 0.001	0.086	0.022
Analysis								
Univariate	8	1.194 (1.078-1.323)	0.001	Random	83.70%	< 0.001	0.063	0.043
Multivariate	4	1.262 (1.025-1.553)	0.028	Random	79.70%	0.002	0.089	0.093
DFS	4	1.092 (0.866-1.377)	0.459	Random	54.90%	0.084	1.000	0.984
RFS/MFS	2	1.513 (1.124-2.038)	0.006	Fixed	0.00%	0.408	1.000	-

OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; MFS, metastasis-free survival; RT-PCR, reverse transcription polymerase chain reaction.

sis by using STATA, version 12.0 (Stata Corporation, College Station, Texas, USA).

Results

Description of the included studies

Searching PubMed, Medline and EMBASE online databases with the key terms resulted in the inclusion of 162 articles published by January 2016. After duplicate publications were removed, 99 articles remained, of which 68 articles were excluded because they were systematic reviews or research using only animals or cells. Among the remaining 31 articles, 19 articles were removed because of the following reasons: 13 without prognostic values and 6 without available data. Finally, 12 articles with a total of 4500 patients were included in this meta-analysis [16, 24, 25, 27, 37-45]. The selection process is shown in the flowchart (**Figure 1**).

The main characteristics of the 12 studies for the meta-analysis are shown in **Table 1**. Because the methods of measuring *H19* expression were different, the threshold values of high and low expression of *H19* were inconsistent. These 12 studies were from different countries: seven studies from China, two studies from the United States, and one study each from Israel, Japan and the Netherlands. Seven types of cancers were included in this analysis: gastric cancer, liver cancer, pancreatic cancer, lung cancer, kidney cancer, bladder cancer, and breast cancer. Six studies calculated HR and 95% CI with univariate analysis, and the other six studies used univariate and multivariate analysis.

Meta-analysis

Eight studies were included to assess the association between *H19* expression and OS in cancer. The random effects model was used to calculate the pooled HR because of a significant heterogeneity across the studies (I^2 = 79.9%, P < 0.001). The pooled HR was 1.167 (95% CI = 1.055-1.291, P = 0.003), indicating that high *H19* expression predicted poor OS in cancer patients (**Table 2**; **Figure 2**).

Four studies were included to evaluate the association between *H19* expression and DFS in cancer. Due to the heterogeneity found across the studies (I^2 = 54.9%, P = 0.084), the

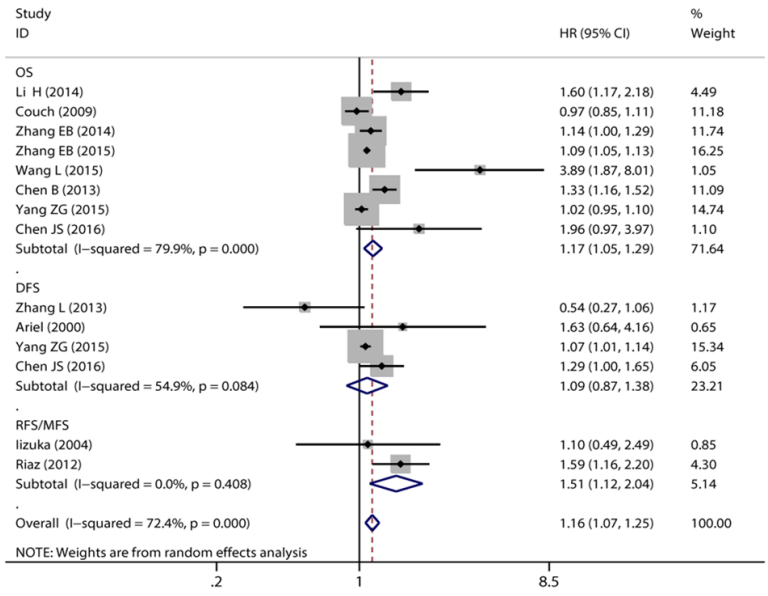

Figure 2. Forest plot of studies evaluating the HR of *H19* in predicting overall survival (OS), disease-free survival (DFS), or recurrence-free survival (RFS)/metastasis-free survival (MFS) in cancer. The central portions and the horizontal lines are HR and the confidence intervals (CIs) and the squares represent the relative weights of the studies. The bottom of the diamonds is the combined HR and confidence interval for subgroup studies. The black solid line is the invalid failure line. There is no statistical significance if the CIs of the pooled HR cross the invalid line.

random effects model was used to calculate the pooled HR. The pooled HR was 1.092 (95% CI = 0.866-1.377, P = 0.459). The results indicated no statistically significant association between *H19* expression and DFS of cancer patients (**Table 2**; **Figure 2**).

Subgroup analysis

In order to identify the potential causes of heterogeneity, subgroup analysis was performed. Regarding OS, subgroup analyses were conducted according to region (China or United States), tumor type (gastric cancer or non-small cell lung cancer), method of measuring *H19* expression (qRT-PCR or others), quality score (< 80% or ≥ 80%), and statistical method (univariate or multivariate).

We detected a significant correlation between elevated expression of *H19* and poor OS in patients with cancer in China (HR = 1.176; 95% CI = 1.045-1.323), but not in the United States (HR = 1.136; 95% CI = 0.833-1.547). Heterogeneity existed across the studies from China and also those from the United States (P < 0.001 and P = 0.001, respectively) (**Figure 3A**). When the type of cancer studied was used for subgroup analysis, a significant correlation was found between high *H19* expression and poor OS in patients with gastric cancer (HR = 1.388; 95% CI = 1.015-1.900). Elevated expression of *H19* had no significant association with prognosis in patients with non-small cell lung cancer (HR = 1.189; 95% CI = 0.977-1.448) (**Figure 3B**). We also performed subgroup analysis with respect to the methods used for measuring *H19* expression. Including only studies that used the RT-PCR method in the meta-analysis did not change the predictive value of *H19* expression in OS of cancer patients (HR = 1.210, 95% CI = 1.039-1.409), and a significant heterogeneity was found among the studies (P < 0.001) (**Figure 3C**).

We then tested the effect of the quality of the published articles and found that including only studies whose scores were higher than 80% did not alter the results of the estimated HR (HR = 1.340, 95% CI = 1.096-1.640). Correlation of *H19* expression with OS was not found in the studies whose scores were lower than 80% (HR = 1.093, 95% CI = 0.925-1.292) (**Figure 3D**). With respect to the different statistical methods used in the studies, we found that studies using univariate analysis and those using multivariate analysis gave similar results regarding the association of *H19* expression with OS (HR = 1.194, 95% CI = 1.078-1.323; HR = 1.262, 95% CI = 1.025-1.553) (**Figure 3E**, **3F**).

Analysis of sensitivity and publication bias

Sensitivity analysis indicated that removing any single study did not alter the predictive value of *H19* in OS and DFS. This finding illustrates that the results of this meta-analysis were stable.

To assess publication bias, the funnel plot was first used as a qualitative measure. The lnHR values and their standard errors were used for the horizontal and vertical axes, respectively.

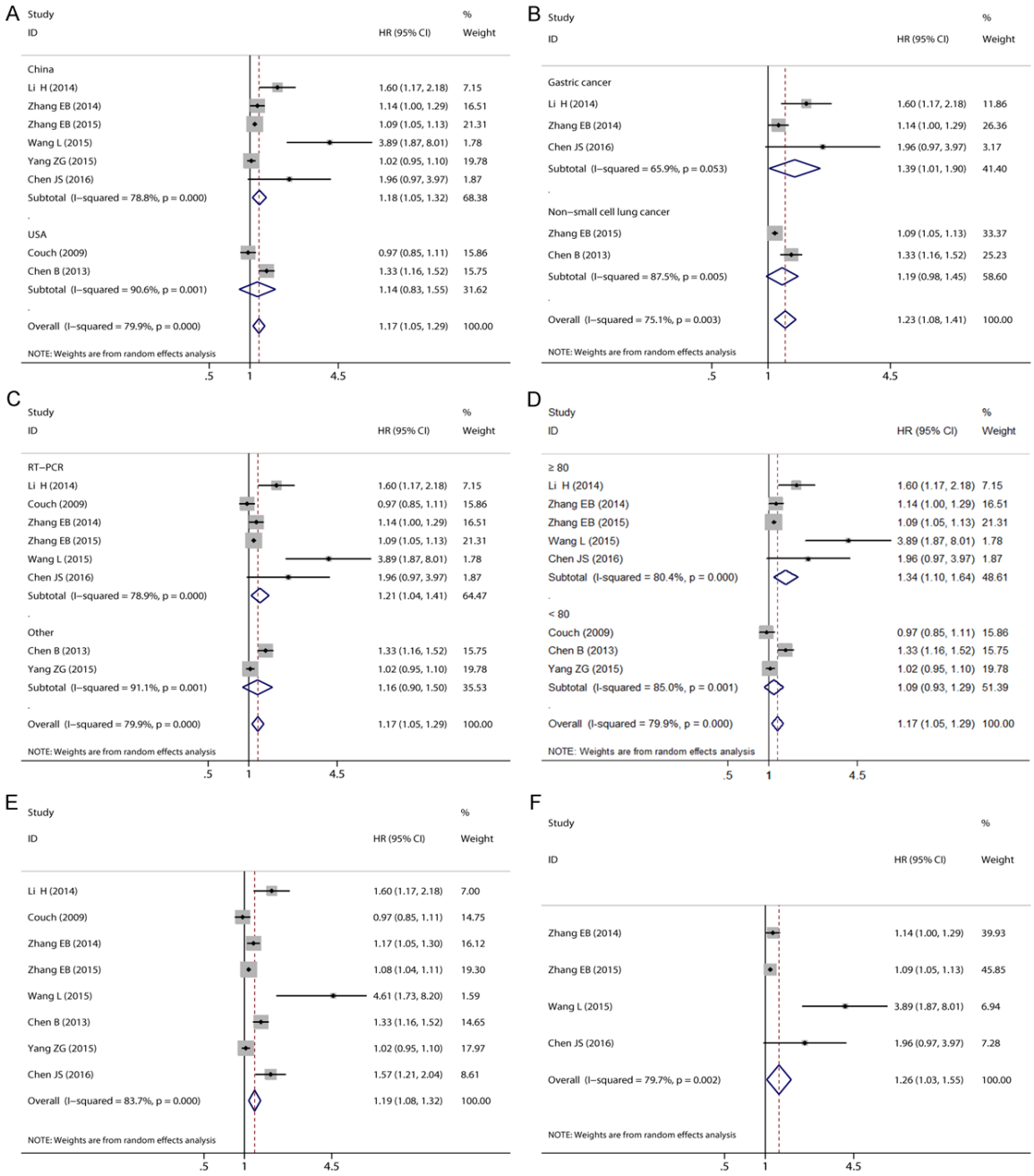

Figure 3. Forest plots of subgroup analysis showing the pooled HRs of elevated *H19* expression in cancer prognosis. The HRs with their 95% CIs of overall survival (OS) were analyzed by the factors of region (A), type of cancer (B), method of measuring *H19* expression (C), quality score (D), univariate analysis (E) and multivariate analysis (F). The central portions of the horizontal line are the confidence intervals (CIs) and the squares represent the relative weights of the studies. The bottom of the diamonds is the combined HR and confidence interval for subgroup studies.

The funnel plot for *H19* and OS was asymmetrical on visual inspection. The Begg rank correlation method and Egger linear regression were used to further assess the publication bias, and the publication bias was found for *H19* and OS (Begg's test p_r > | z | = 0.063; Egger's test P > | t | = 0.075) (**Figure 4A**). Next, we considered there existed some "missing" studies which cause the funnel plot asymmetry. The trim and fill sensitivity analysis was used to

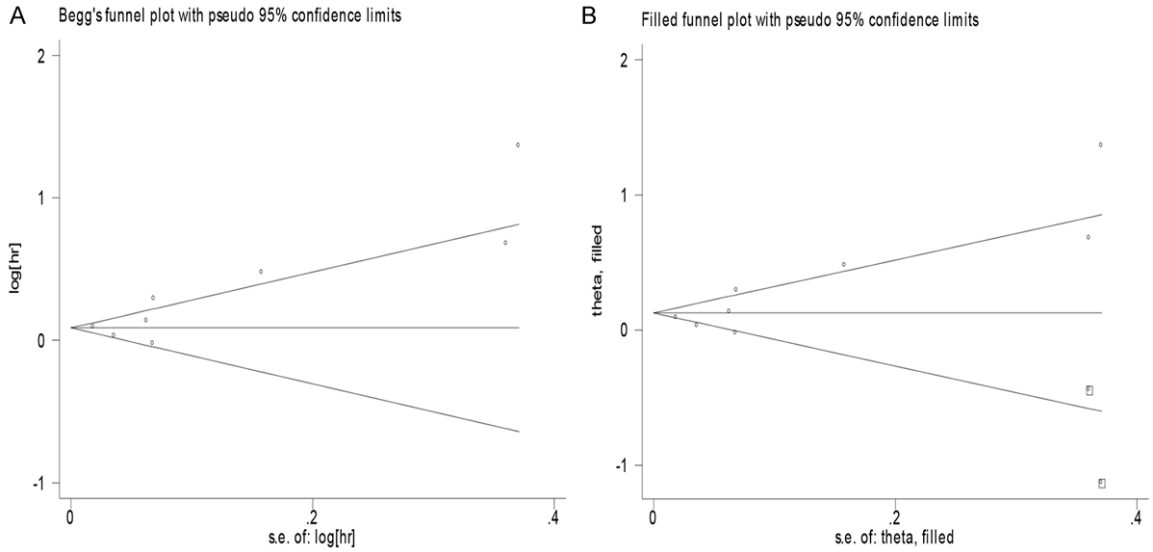

Figure 4. Begg's funnel plot for the analysis of the prognostic value of *H19* in overall survival (OS) of patients with cancer. A. Funnel plot of publication bias for the analysis of the pooled HRs of *H19* expression with OS. B. The adjusted funnel plot for publication bias.

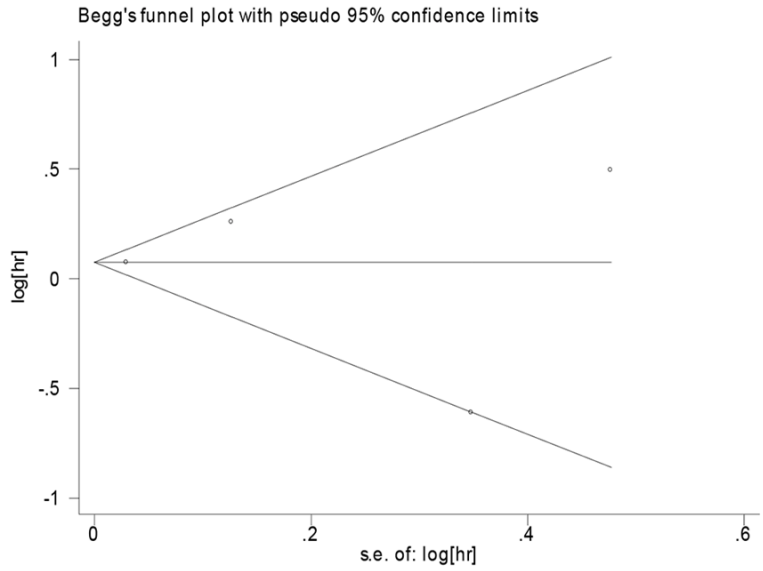

Figure 5. Funnel plot of publication bias for the analysis of the independent role of *H19* in disease-free survival (DFS) in cancer.

impute their HRs incorporates the hypothetical missing studies as though they actually existed. The results showed a statistically significant association between *H19* expression and OS in cancer (HR = 1.134, 95% CI = 1.014-1.269, *P* = 0.028), which indicating that the stability of our results (**Figure 4B**). However, no obvious publication bias was observed for DFS in cancer patients, Begg's test p_r > | z | = 1.000; Egger's test *P* > | t | = 0.984 (**Figure 5**).

Discussion

LncRNAs play an important role in regulating gene expression, cell growth and metabolism, tumor metastasis and invasion, and survival of cancer patients. Numerous studies have shown that differential expression of *H19* between tumor tissue and adjacent normal tissue is closely correlated with tumor development, progression, metastasis, invasion, and prognosis [5, 21, 26, 46]. However, the role of *H19* in cancer was still not clear. Previous studies have shown that *H19* acts as an oncogene in tumors [21, 46, 47]. The influence of *H19* expression on the prognosis of tumor patients' survival was still not clear. This is the first meta-analysis to evaluate the association between the expression of *H19* and prognosis of cancer patients; it will provide some scientific basis for predicting patient survival.

The function of *H19* in tumorigenesis and metastasis has been studied in many types of cancers. Zhang *et al* [24] found that high

expression of *H19* correlated with poor prognosis of NSCLC patients. *H19* was up-regulated in NSCLC cells via activation by c-Myc. Zhou *et al* [48] reported that *H19* and miR-657 expression in the plasma of patients with gastric cancer was significantly higher than in the plasma of normal subjects. After the plasma samples were placed in an incubator at room temperature for 0, 6, 24 hours, the level of miR-657 decreased, while *H19* level was stable, indicating that *H19* was more suitable than miR-657 as a target for the diagnosis of gastric cancer. Another study reported that *H19* expression in HCC patients was increased, with multivariate Cox regression analysis HR = 1.017 (95% CI = 1.01-1.137, P = 0.022), indicating that *H19* expression was predictive of poor survival for HCC patients [27]. Furthermore, *H19* and miR-675 could promote the aggressive phenotype in breast cancer cells, accelerating breast cancer cell proliferation and migration in vitro and tumor growth and metabolism in vivo [26]. In addition, *H19* played a pivotal role in tumor proliferation in esophageal squamous cell carcinoma (ESCC) [49]. Thus *H19* gene may be used as a tumor marker to predict the survival of cancer patients. However, Zhang *et al* [39] found that *H19* expression in HCC was significantly lower than in the adjacent tissues, and low expression was correlated with poor prognosis. Furthermore, cellular experiments showed that *H19* inhibited hepatoma cell metastasis and reversed epithelial mesenchymal transition. The possible mechanism was that *H19* bound with the protein complex HnRNP U/PCAF/RNA PolII to activate the miR-200 family, which in turn inhibited the invasion and metastasis of liver cancer cells. These studies suggest that *H19* plays a role in tumorigenesis and can be used as a gene target for cancer treatment.

The current meta-analysis summarized the results of 12 studies with a total of 4500 patients. There were 8 studies associated with overall survival in cancer patients. The pooled HR of OS (1.167, 95% CI = 1.055-1.291, P = 0.003) showed that statistical significance was found between the expression of *H19* and OS, and indicated that high expression of *H19* was predictive of poor patient survival in cancer. Among those 8 studies, 3 studies showed that there was no significant association between *H19* expression and OS in cancer patients; it is likely that the methods they used for measuring *H19* expression contributed to this discrepancy [27, 42, 45]. Subgroup analysis was conducted between *H19* expression and OS in cancer patients, and the results showed that region, tumor type, method of measuring *H19* expression, quality score, and statistical method did not affect the prognostic value of *H19* in OS, but heterogeneity still existed across these studies. Furthermore, the funnel plot, Begg's and Egger's test indicated the possibility of publication bias. The results of trim and fill method did not change the predictive value of *H19* expression in OS of cancer patients, it further demonstrated the stability of the general results. The prognosis value of *H19* in DFS was included in 4 studies, and the results showed no correlation between *H19* expression and DFS. The lack of correlation may be attributed to the absence of sufficient samples or that the quality of the included studies was low.

Although this meta-analysis study was conducted in accordance with strict inclusion and exclusion criteria, there were still limitations in this analysis. First, almost all of the studies included were retrospective studies and the number of studies included was small. Second, because some pooled HRs were extracted from Kaplan-Meier survival curves, inaccuracy may occur when reading survival rates. Third, experimental methods used in the included studies were different, and it may cause potential bias. Although we had tried to collect all the relevant data, some of the missing data may reduce the reliability of the analysis. Therefore, in order to further clarify *H19*'s impact in terms of tumor prognosis, high quality studies should be conducted.

In conclusion, the results of the current meta-analysis showed that high expression of *H19* indicated a poor prognosis in patients with cancer.

Acknowledgements

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Disclosure of conflict of interest

None.

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