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Altered long noncoding RNAs and survival outcomes in ovarian cancer
A systematic review and meta-analysis (PRISMA Compliant)

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Abstract

Background: Previous studies investigating the association between altered long noncoding RNAs (lncRNAs) and survival outcomes in ovarian cancer have obtained controversial results. To comprehensively evaluate the association, we conducted a systematic review and meta-analysis of the studies published on the subject.

Methods: We performed a systematic search using the databases of the Cochrane Central Register of Controlled Trials, PubMed, and Embase to find all relevant articles from inception to May 7, 2017. Studies that evaluated the association between 1 specific lncRNA and survival outcomes in ovarian cancer were included. Pooled hazard ratios (HRs) and 95% confidence intervals (95% CIs) for overall survival, progression-free survival, and disease-free survival were calculated with a fixed-effects or random-effects model.

Results: A total of 15 studies involving 1333 patients with ovarian cancer were included in this meta-analysis. Altered lncRNAs were associated with decreased overall survival (HR: 2.29, 95% CI: 1.92–2.75) without heterogeneity ($I^2 = 0.0\%$) in ovarian cancer. Altered lncRNAs were also associated with decreased progression-free survival (HR: 2.77, 95% CI: 1.00–7.62, $I^2 = 76.6\%$) and disease-free survival (HR: 2.59, 95% CI: 0.89–7.57, $I^2 = 62.9\%$) in ovarian cancer.

Conclusion: Our results supported the strong prognostic value of altered lncRNAs in ovarian cancer. Further large-scale studies should be carried out to verify the clinical applications of altered lncRNAs in the prognosis assessment of ovarian cancer.

Abbreviations: CI = confidence interval, DFS = disease-free survival, DSS = disease-specific survival, HR = hazard ratio, LncRNAs = long noncoding RNAs, NOS = Newcastle–Ottawa scale, OS = overall survival, PFS = progression-free survival.

Keywords: long noncoding RNA, meta-analysis, ovarian cancer, survival outcome

1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related death in women worldwide, with 22,280 estimated new cases and 14,240 estimated deaths in the United States alone in 2016.[1] As early-stage ovarian cancer is generally asymptomatic and sensitive screening method is still not available, almost 65% of patients with ovarian cancer are diagnosed at advanced stages.[2] Despite recent advances in surgical techniques and pharmaceutical treatment, the 5-year survival rate of ovarian cancer has not improved accordingly, remaining less than 30%.[3] In order to

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improve the survival of patients with ovarian cancer, it is imperative to identify effective prognostic factors to predict the survival outcomes. It has been revealed that clinicopathological parameters, such as tumor histology, tumor stage, and residual tumor diameter, are independent prognostic factors for ovarian cancer.[4] However, even for patients with similar status and treatment, the survival outcomes can be different from each other. The underlying mechanism of ovarian cancer is a complicated biological process involving genetic and epigenetic alterations.[5,6] Thus, identifying molecular prognostic factors may enable more accurate prediction of patients' outcomes and bring novel therapeutic targets.

After decades of studying on RNA biology, long noncoding RNAs (lncRNAs) have been identified as significant regulators involved in various biological processes.[7] LncRNAs are RNA molecules longer than 200 nucleotides and possess no or little protein coding abilities due to their lacking of open reading frames.[8] They can modulate gene expression at the transcriptional, post-transcriptional, and epigenetic levels.[9] It has been found that lncRNAs not only play crucial roles in multiple physiological processes but also participate in various pathological conditions, including cancer.[10] Interestingly, preclinical studies have found that lncRNAs, such as PVT1 and H19, can exert carcinogenic effects via inducing tumor cell proliferation, invasion and migration, and inhibiting tumor cell apoptosis.[11,12] These effects have also been shown in ovarian cancer derived cell lines.[13,14] Accordingly, a body of epidemiologic studies has revealed that altered lncRNAs were associated with poor survival outcomes in several malignancies, including breast, gastric, and colorectal cancer.[15–17]

A number of studies have investigated the relationship between altered lncRNAs and survival outcomes in ovarian cancer; however, the results are inconsistent. Thus, we performed a systematic review based on available evidence to determine whether altered lncRNAs were associated with poor survival outcomes in ovarian cancer.

2. Methods

This meta-analysis was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18] As this study was a review of previous published studies, ethical approval or patient consent was not a requirement.

2.1. Search strategy

We performed a systematic search using the databases of the Cochrane Central Register of Controlled Trials, PubMed, and Embase to find all relevant articles from inception to May 7, 2017. Both subject headings and free text words were used in the search. The detailed search strategies are presented in Appendix A, http://links.lww.com/MD/C378. In addition, the reference lists from all retrieved articles were screened for additional eligible studies. There was no language restriction in our search strategy.

2.2. Eligibility criteria

After conducting the search, 2 independent reviewers removed duplicates and screened the titles and abstracts. Then, they evaluated potentially relevant references in detail to determine the eligibility. Studies that met the following inclusion criteria were included in this meta-analysis: evaluated the association between 1 specific lncRNA and survival outcomes in ovarian cancer; evaluated at least 1 of the outcomes of interest, including overall survival (OS), progression-free survival (PFS), disease-specific survival (DSS), and disease-free survival (DFS); and reported HR and a 95% CI or provided data for their calculation. Articles were excluded if they were reviews, editorials, letters, and case reports; without appropriate data that could be extracted or calculated; and used microarray data. In cases of duplicate publications involving the same population, only the most comprehensive one was included. Any disagreements in study selection were resolved by discussion between the 2 reviewers and, if needed, in consultation with a third reviewer.

2.3. Data extraction and quality assessment

Two reviewers extracted data independently. The following data were collected from each study: publication data (i.e., first author's name, publication year, and study location), specimen, sample size, detective method, internal reference, follow-up, HR and 95% CI, and covariants. When multiple estimates of effect (HR) were presented, the most adjusted one was extracted; when adjusted estimate was not available, crude estimate was extracted. When the HR and 95% CI were not available, we estimated them indirectly from Kaplan–Meier curves using published methods.[19,20]

Three reviewers evaluated the methodological quality of included studies independently. The quality was assessed using the Newcastle–Ottawa scale (NOS).[21] The NOS uses a star system ranging from 0 to 9 stars. Studies that awarded 7 or more stars were considered high quality.

2.4. Statistical analysis

The pooled HR was obtained by combing the HRs from individual eligible study. Heterogeneity was measured using the Chi-square (χ^2, or Chi^2) and I^2 test. When significant heterogeneity ($P < .10$ or $I^2 > 50\%$) was found, a random-effects model was applied to calculate the pooled effect; otherwise, a fixed-effects model was used. All analyses were performed using Stata version 12.0 software (Stata Corporation, College Station, TX). For all tests, a 2-sided P value less than .05 was considered statistically significant.

3. Results

3.1. Study selection

In our initial search, 345 records were identified from the database search. After removing duplicates and screening the titles and abstracts, 27 potentially relevant records were retrieved for further review. Of these, 12 studies were excluded for following reasons: 6 did not have usable data,[22–27] 1 did not report any outcomes of interest,[28] and 5 used microarray data.[29–33] We retrieved no additional studies from reference lists. Finally, 15 studies that met our eligibility criteria were included in the meta-analysis.[14,34–47] The flow diagram summarizing the process of study selection is given in Fig. 1.

3.2. Study characteristics

A total of 15 studies involving 1333 patients with ovarian cancer were included in the meta-analysis. The studies were published
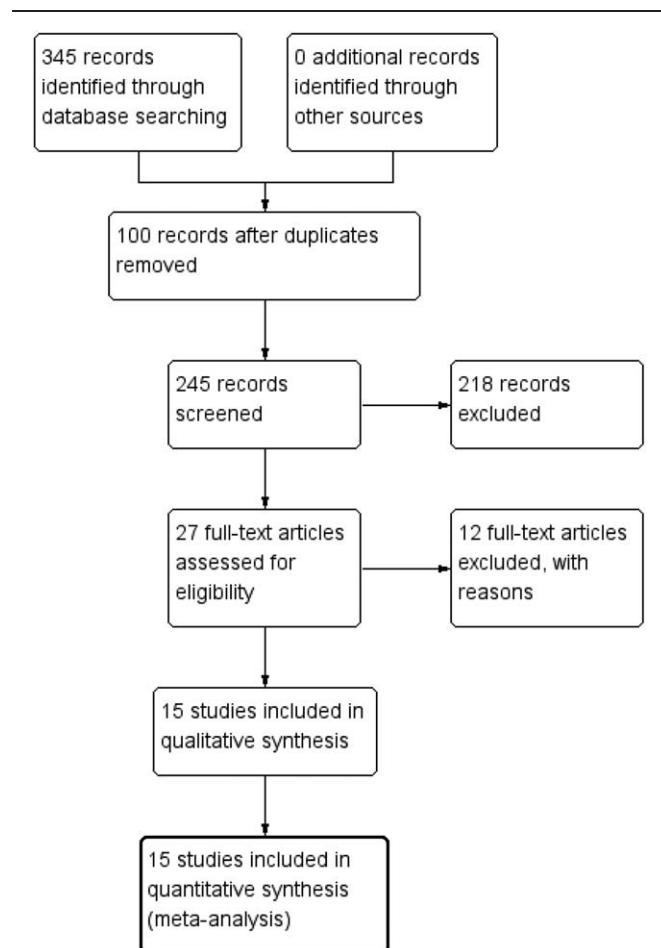

Figure 1. Study flow diagram.

Table 1

Characteristics of included studies.

Ref.	Study location	Study design	Sample size (high/low)	Specimen type	LncRNAs Signature	LncRNAs Expression	Detective method	Internal reference	Covariant*	Follow up, mo	Outcome	HR and 95% CI availability	Quality score
Qiu et al[34]	China	R	64 (32/32)	Tissue	HOTAIR	Upregulated	qRT-PCR	GAPDH	1–4	9–79	OS, DFS	Directly	8
Qiu et al[35]	China	R	64 (32/32)	Tissue	TC0101441	Upregulated	qRT-PCR	GAPDH	1,2,5	49–84	OS	Directly	8
Cheng et al[36]	China	R	75 (38/37)	Tissue	AB073614	Upregulated	qRT-PCR	GAPDH	Unclear	60	OS	Indirectly	4
Qiu et al[37]	China	R	68 (34/34)	Tissue	ANRIL	Upregulated	qRT-PCR	GAPDH	1,2,3,4	49–89	OS	Directly	8
Qiu et al[37]	China	R	68 (34/34)	Tissue	HOTAIR	Upregulated	qRT-PCR	GAPDH	1,2,3	49–89	OS	Directly	8
Chen et al[38]	China	R	94	Plasma	MALAT1	Upregulated	qRT-PCR	β-actin	2, 4,6–8	Unclear	OS	Directly	7
Chen et al[39]	China	R	149 (74/75)	Tissue	NEAT1	Upregulated	qRT-PCR	GAPDH	1,2,9	60	OS	Directly	8
Huang et al[40]	China	R	109 (55/54)	Tissue	CCAT2	Upregulated	qRT-PCR	GAPDH	1,2,9	Unclear	OS, DFS	Indirectly	7
Qiu et al[41]	China	R	102 (51/51)	Tissue	ANRIL	Upregulated	qRT-PCR	GAPDH	1–3	49–89	OS	Directly	8
Yang et al[42]	China	R	53 (27/26)	Tissue	UCA1	Upregulated	qRT-PCR	GAPDH	4	Unclear	OS	Directly	7
Yim et al[43]	Korea	R	129 (27/102)	Tissue	HOXA11as	Upregulated	qRT-PCR	U6	1–4,10	2–116	OS, PFS	Direclty	7
Zhang et al[44]	China	R	117 (59/58)	Tissue	UCA1	Upregulated	qRT-PCR	RUN6	1,4	14.9–29.1	OS	Directly	8
Li et al[45]	China	R	124 (62/62)	Tissue	SPRY4-IT1	Upregulated	qRT-PCR	GAPDH	1,2,4	Unclear	OS, PFS	Directly	7
Xia et al[46]	China	R	60 (30/30)	Tissue	ZFAS1	Upregulated	qRT-PCR	β-actin	Unclear	Unclear	OS	Indirectly	5
Yan et al[47]	China	R	57 (28/29)	Tissue	NBAT-1	Downregulated	qRT-PCR	GAPDH	Unclear	12–60	OS	Indirectly	7

DFS = disease-free survival, LncRNAs = long noncoding RNAs, OS = overall survival, PFS = progression-free survival, R = retrospective study.
* 1, FIGO stage; 2, histological grade; 3, residual tumor diameter; 4, lymph node metastasis; 5, TC0100223 expression; 6, TNM stage; 7, peritoneal invasion; 8, serum carbohydrate antigen 125; 9, distant metastasis; 10, age; 11, chemotherapy response.

between 2014 and 2017. Of these, 14 studies were carried out in China[14,34–42,44–47] and 1 in Korea.[43] Fourteen of our included studies were carried out using human tissues[14,34–37,39–47] and 1 using plasma.[38] A total of 12 different lncRNAs were linked with survival outcomes in ovarian cancer. The expression of lncRNAs was upregulated in 14 studies[14,34–46] and down-regulated in 1 study.[47] OS, PFS, and DFS were investigated to evaluate survival outcomes in 15 (100.0%), 2 (13.3%), and 2 (13.3%) studies, respectively. The NOS values ranged from 4 to 8 stars: 1 study was awarded 4 stars,[36] 1 study was award 5 stars,[46] and 13 studies were award 7 or more

stars.[14,34,35,37–45,47] The characteristics of the included studies are summarized in Table 1.

3.3. Meta-analysis of OS

We first investigated the prognostic value of altered lncRNAs for OS in all 15 included studies. The pooled data indicated that altered lncRNAs were associated with decreased OS (15 studies, 1333 patients, HR: 2.29, 95% CI: 1.92–2.75). The Cochran Q test had a P value of .61, and the quantity I^2 was 0.0%, both indicating no significant heterogeneity among the 15 included studies (Fig. 2).
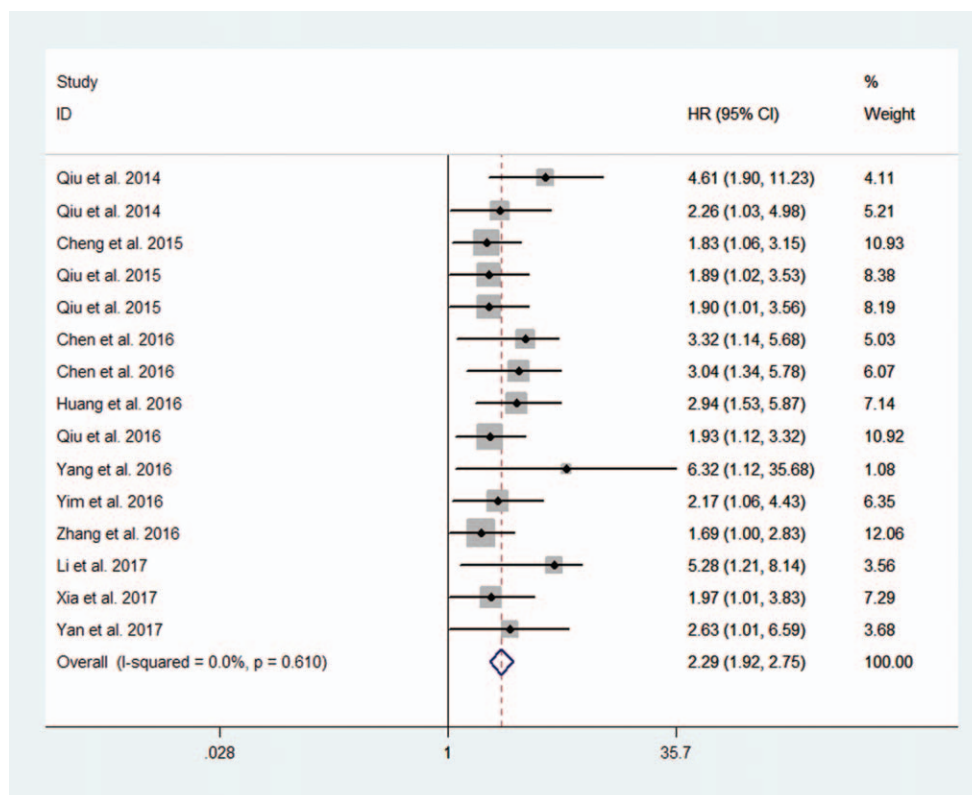

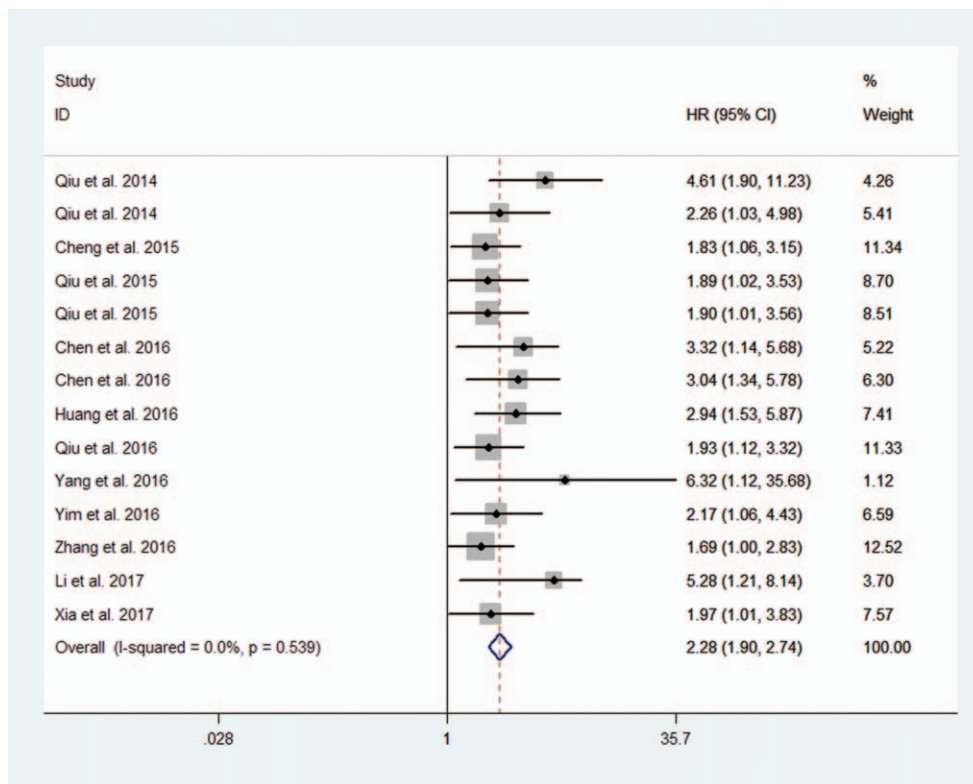Figure 2. Forest plot of altered lncRNAs and overall survival.

Figure 3. Forest plot of upregulated lncRNA signatures and overall survival.

Then, we performed a subanalysis based on the exact expression pattern of lncRNAs in ovarian cancer specimens compared with normal controls. The expression of lncRNAs was upregulated in 14 studies involving 1276 patients with ovarian cancer.[14,34–46] The estimated pooled HR showed that upregulated lncRNA signatures were associated with decreased OS (14 studies, 1276 patients, HR: 2.28, 95% CI: 1.90–2.74). The Cochran Q test had a P value of .539, and the quantity I^2 was 0.0%, both of which indicated no significant heterogeneity among the 14 studies (Fig. 3). As only 1 study investigated the association between downregulated lncRNA signature and OS, we were unable to perform an accordingly meta-analysis. In the study by Yan et al,[47] the lncRNA NBAT-1 was downregulated in OC specimens compared with normal controls and was associated with a poor outcome of OC (HR: 2.626, 95% CI: 1.01–6.59).

3.4. Meta-analysis of PFS

The prognostic value of altered lncRNAs in PFS was evaluated in 2 studies with 253 patients.[43,45] The estimated pooled HR indicated that altered lncRNAs were associated with decreased PFS (2 studies, 253 patients, HR: 2.77, 95% CI: 1.00–7.62). The Cochran Q test had a P value of .039, and the quantity I^2 was 76.6%, both indicating significant heterogeneity between these 2 studies (Fig. 4).

3.5. Meta-analysis of DFS

The prognostic value of altered lncRNAs in DFS was evaluated in 2 studies with 173 patients.[34,40] The pooled HR indicated that altered lncRNAs were associated with decreased DFS, though the

data supporting this association were not as robust (2 studies, 173 patients, HR: 2.59, 95% CI: 0.89–7.57). The Cochran Q test had a P value of .101, and the quantity I^2 was 62.9%, both indicating significant heterogeneity between these 2 studies (Fig. 5).

4. Discussion

This present meta-analysis supported for a strong association between altered lncRNAs and poor survival outcomes in ovarian cancer. In this meta-analysis of 15 studies, we found that patients with ovarian cancer who had altered lncRNAs showed decreased OS, PFS, and DFS, which is in accordance with the promising findings derived from in vitro studies.[13,14] In addition, our results were in accordance with several other meta-analyses with regard to the association between altered lncRNAs and survival outcomes in cancers of other specific sites. Likewise, they found that altered lncRNAs were associated with poor survival outcomes in renal cell carcinoma, osteosarcoma, and hepatocellular carcinoma.[48–50] Luo et al[51] also performed a meta-analysis to investigate the prognostic value of abnormally expressed lncRNAs in ovarian cancer. In their study, 2 studies using microarray data were included[29,31]; however, we did not include any studies using microarray data. Moreover, while they only performed the meta-analysis of OS, we also performed the meta-analysis of PFS and DFS.

Among the altered lncRNA profiles, 11 lncRNAs, including HOTAIR, TC010441, AB073614, ANRIL, MALAT1, NEAT1, CCAT2, UCA1, HOXA11as, SPRY4-IT1, and ZFAS1, were significantly increased in patients with ovarian cancer, suggesting that these lncRNAs may play oncogenic roles in ovarian cancer development.[14,34–46] However, the expression of some of the
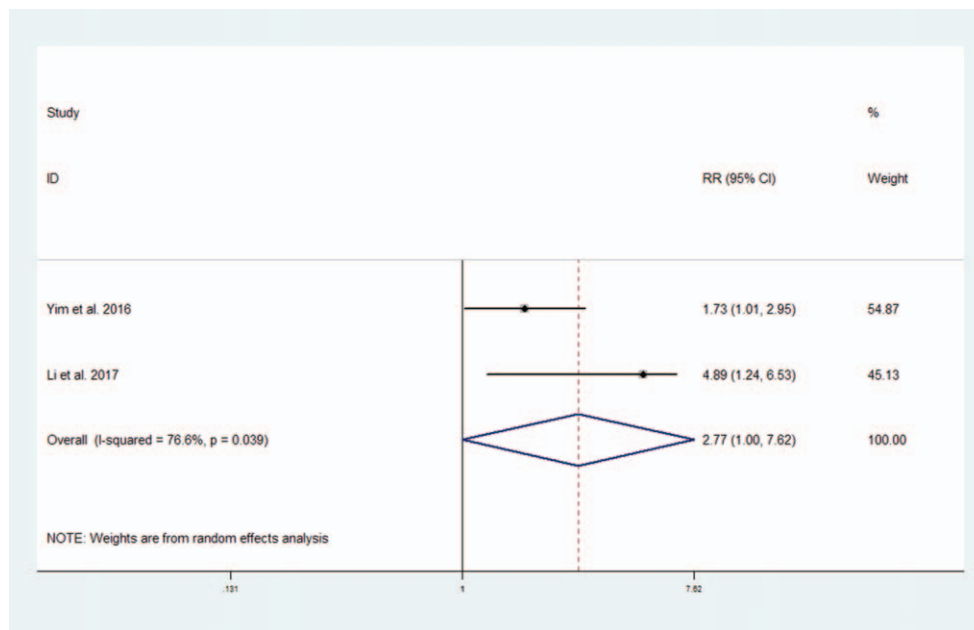
Figure 4. Forest plot of altered lncRNAs and progression-free survival.

above lncRNAs, such as SPRY4-IT1, was decreased in gastric cancer and was associated with a poor prognosis in such disease.[52] On the contrary, the expression of lncRNA NBAT-1 was significantly decreased in patients with ovarian cancer and was associated with a poor prognosis.[47] These findings suggest that the expression of lncRNAs might be tissue-specific, and they play different and distinct roles in cancer development.

LncRNAs have been shown to participate extensively in tumor initiation, progression, and metastasis during the development of ovarian cancer. For example, the lncRNA NEAT1 can regulate carcinogenesis and progression of ovarian cancer via interactions

with HuR and miR-124–3p and may therefore serve as a potential antineoplastic therapeutic target.[53] In addition, the lncRNA TUG1 can promote ovarian cancer metastasis by affecting the epithelial-mesenchymal transition.[54] Abnormal expression of HOTAIR is associated with chemoresistance in ovarian cancer.[55] HOTAIR can interact with polycomb repressive complex 2 (PRC2) and is essential for histone H3 lysine-27 trimethylation of the HOD locus32.[56]

In our analysis, a strength deserved to be mentioned is that no significant heterogeneity was present in meta-analysis of OS. This reinforced the reliability of our pooled results. Still, there are
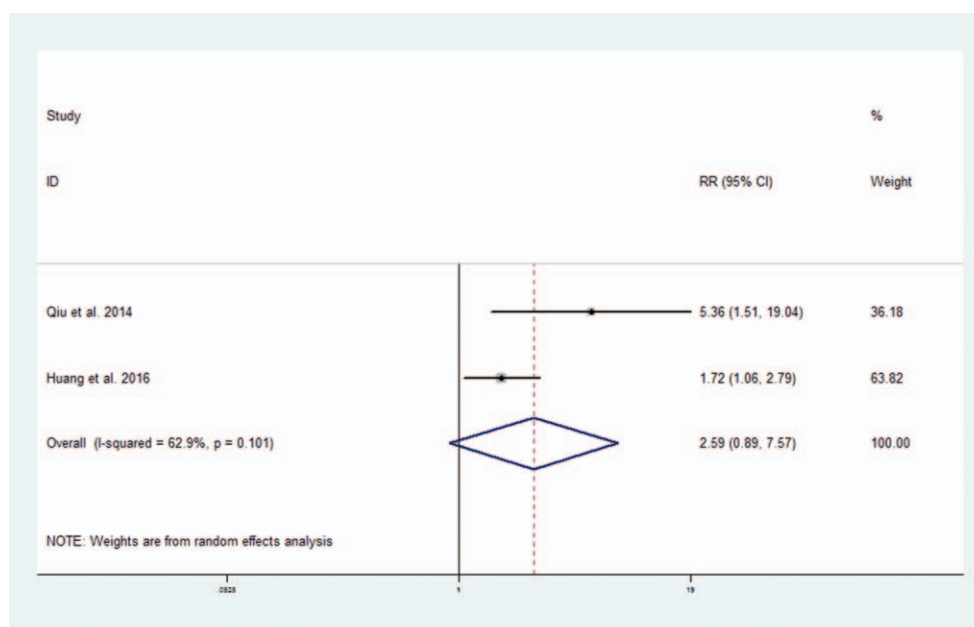

Figure 5. Forest plot of altered lncRNAs and disease-free survival.

several limitations in our analysis that should be noted. First, several lncRNAs were included to evaluate their prognostic value in ovarian cancer; however, a specific ovarian cancer related lncRNA was absent for clinical assessment. Second, the probable action mechanism of lncRNAs has not been clarified yet. Third, on some occasions, we calculated HRs ourselves on the basis of the data provided in the article, which may not be the most accurate estimate of HR. However, significant difference has not been shown yet comparing our calculation with direct estimation of HR. Fourth, as most patients enrolled in this meta-analysis were Chinese and the total sample size was relatively small, the overall result of this study may not be able to be extended to all populations. As a result, in order to confirm these results, multicenter and larger-size studies investigating the prognostic value of lncRNAs in ovarian cancer should be conducted in the future.

5. Conclusion

Our results supported the strong prognostic value of altered lncRNAs in ovarian cancer. Further large-scale studies should be carried out to verify the clinical applications of altered lncRNAs in the prognosis assessment of ovarian cancer.

Author contributions

NL: study design, literature search, systematic review and data collection, statistical analysis, interpretation of results, and preparation of the manuscript; H-YC and WS: a contribution to critical review of the manuscript; L-JH: checked and corrected the typographical and grammatical errors, and confirmed all contributing authors gave permission to be named.
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Software: Yingchao Hu.
Validation: Shu Wang.
Writing – original draft: Li Ning.
Writing – review & editing: Jinghe Lang.
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