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The Impact of lncRNA Dysregulation on Clinicopathology and Survival of Breast Cancer: A Systematic Review and Meta-analysis

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Dysregulation of multiple long non-coding RNAs (lncRNAs) was reported to play major roles in breast cancer (BC). Here we aimed to collect most of the relevant literature to assess the prognostic value of lncRNAs in BC. To this end, we systematically searched PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Wanfang to identify published articles on the associations of lncRNAs with clinicopathology and/or survival of BC. Via this searching, we identified 70 articles involving 9,307 BC patients and regarding 48 lncRNAs. The expression of 41 lncRNAs was related to one or more clinicopathological parameters of BC, including tumor size; lymph node metastasis; histological grade; TNM stage; and estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) statuses ($p < 0.05$). Dysregulation of 28 lncRNAs was associated with overall survival, and abnormal expression of 9 lncRNAs was linked to disease-free survival. Furthermore, the expression level of 3 lncRNAs was correlated with metastasis-free survival, 3 lncRNAs with relapse-free survival, and 3 lncRNAs with progression-free survival. Our analysis showed that multiple lncRNAs were significantly associated with BC clinicopathology and survival. A large-scale study is needed to verify the prognostic value of these lncRNAs in BC.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women and the main cause of female cancer death in the world.[1] Although the survival rates of BC have been improved by early detection and progress in treatment, it remains to be a frequent malignancy with a poor prognosis, which seriously threatens the health of women.[2,3]

Traditionally, we used clinicopathological features, including tumor size, lymph node status, TNM stage, histological grade, hormone receptor status, and human epidermal growth factor receptor 2 (HER-2) amplification, to predict the patient outcome.[4] In addition, several biomarkers, such as tumor-associated macrophages (TAMs), microRNAs, matrix metalloproteinases (MMPs), retinoic acid receptor α (RARA), Ki-67, aromatase, osteopontin, etc., have also been identified.[5–8]

In recent years, more and more BC studies have focused on long non-coding RNAs (lncRNAs) because of their key roles in human diseases, including cancer.[9]

lncRNAs are a class of RNA transcripts, with a length of >200 nt, that do not encode proteins. They were proven to be involved in diverse biological processes, such as chromosome remodeling, epigenetic modulation, and transcriptional and posttranscriptional modifications.[10,11] Studies have revealed that lncRNAs play an important role in cancer biology, and the expression of specific lncRNAs is implicated in the development and progression of cancer.[12] For example, enforced expression of HOTAIR in epithelial cancer cells can induce genome-wide re-targeting of polycomb repressive complex 2 (PRC2), leading to altered histone H3 lysine 27 methylation and gene expression, and thus it promotes cancer invasiveness and metastasis in a manner dependent on PRC2.[13] In BC, *BCAR4* can bind to two transcription factors (SNIP1 and PNUTS) with extended regulatory consequences, and it relieves inhibition of RNA polymerase II (Pol II) via activation of the PP1 phosphatase. Thus, it activates a noncanonical Hedgehog/GLI2 pathway that promotes cell migration.[14] Moreover, a large number of lncRNAs, such as *MALAT1*, *MEG3*, *HOTAIR*, *CCAT2*, *H19*, etc., are dysregulated in multiple tumors, including BC, hepatocellular carcinoma, and kidney cancer, possibly making them diagnostic or prognostic biomarkers or potential therapeutic targets for cancer.[15–17]

Many studies on the role of lncRNAs in BC revealed that the expression level of lncRNAs was associated with BC clinical features and

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Table 1. Characteristics of Studies Included in the Meta-analysis

lncRNAs	Reference	Country	Race	Number of Patients	Expression in Tumor	Method	Sample Type	Cutoff	Survival	Follow-up (Month)	Quality Score
MALAT1	[26]	China	Asian	43	upregulated	qRT-PCR	tissue	median	OS	60	7
	[25]	China	Asian	118	upregulated	qRT-PCR	tissue	NR	OS	50	7
	[20]	France	Caucasian	446	upregulated	qRT-PCR	tissue	3.02-fold	NR	NR	7
	[24]	China	Asian	139	upregulated	qRT-PCR	tissue	median	OS	55	7
	[22]	China	Asian	204	upregulated	qRT-PCR	tissue	75% expression	RFS	65	8
	[21]	China	Asian	135	downregulated	qRT-PCR	tissue	NR	NR	NR	6
	[23]	China	Asian	78	upregulated	qRT-PCR	tissue	median	DFS	60	8
	[27]	China	Asian	86	upregulated	qRT-PCR	tissue and serum	median	OS	NR	5
CCAT2	[31]	China	Asian	120	upregulated	qRT-PCR	tissue	NR	OS	90	6
	[32]	Iran	Caucasian	48	normal	qRT-PCR	tissue	median	NR	NR	6
	[81]	Netherlands	Caucasian	747	upregulated	qRT-PCR	tissue	quartile	OS, MFS	>120	7
	[80]	China	Asian	67	upregulated	qRT-PCR	tissue	8-fold	OS	60	7
	[82]	Germany	Caucasian	129	NR	qRT-PCR	tissue	median	MFS	120	8
HOTAIR	[13]	America	Caucasian	132	upregulated	qRT-PCR	tissue	125-fold	OS, MFS	180	8
	[83]	Denmark	Caucasian	488	NR	microarray	tissue	median	MFS	217	7
	[84]	Italy	Caucasian	336	NR	qRT-PCR	tissue	mean	OS, RFS	86	8
	[85]	China	Asian	30	NR	qRT-PCR	tissue	median	OS	40	5
	[44]	America	Caucasian	94	NR	ISH	tissue	median	NR	NR	6
	[43]	China	Asian	112	upregulated	qRT-PCR	serum	median	DFS	48	7
MEG3	[28]	China	Asian	90	downregulated	qRT-PCR	tissue	NR	OS, DFS	80	6
	[29]	China	Asian	207	downregulated	qRT-PCR	tissue	median	OS, PFS	60	8
	[30]	China	Asian	257	downregulated	qRT-PCR	tissue	$\Delta Ct = 8.065$	OS, RFS	60	8
TUSC7	[33]	China	Asian	31	downregulated	qRT-PCR	tissue	mean	NR	NR	6
	[34]	China	Asian	42	downregulated	qRT-PCR	tissue	median	NR	NR	6
BCAR4	[35]	Germany	Caucasian	96	NR	qRT-PCR	tissue	NR	NR	NR	6
	[36]	Netherlands	Caucasian	786	NR	qRT-PCR	tissue	detection limit	OS, PFS, MFS	97	8
TP73-AS1	[37]	China	Asian	86	upregulated	qRT-PCR	tissue	median	NR	NR	8
	[38]	China	Asian	36	upregulated	qRT-PCR	tissue	median	OS	48	8
NEAT1	[40]	China	Asian	118	upregulated	qRT-PCR	tissue	NR	OS	60	6
	[39]	China	Asian	70	upregulated	qRT-PCR	tissue	NR	OS	60	6
	[86]	China	Asian	40	upregulated	qRT-PCR	tissue	2-fold	OS	24	6
TUG1	[41]	China	Asian	100	upregulated	qRT-PCR	tissue	mean	NR	NR	7
	[42]	China	Asian	58	downregulated	qRT-PCR	tissue	mean	NR	NR	6
CRNDE	[46]	China	Asian	103	upregulated	qRT-PCR	tissue	NR	OS	NR	6
	[45]	China	Asian	76	upregulated	qRT-PCR	tissue& serum	$2^{-\Delta\Delta Ct} = 1$	NR	NR	6

OS, overall survival; DFS, disease-free survival; MFS, metastasis-free survival; RFS, relapse- free survival; PFS, progression-free survival; NR, not report; ISH, *in situ* hybridization.

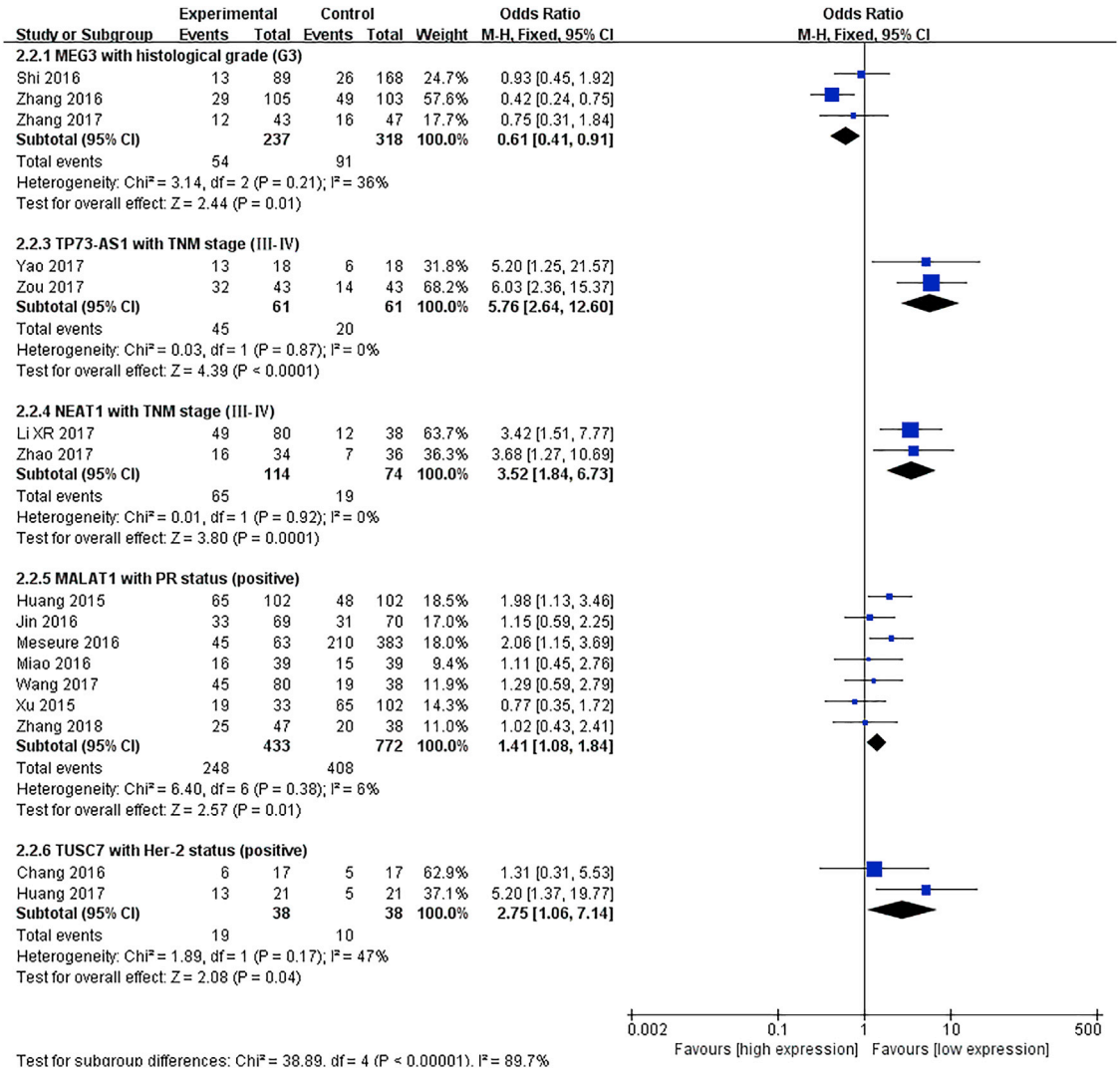

Figure 1. Forest Plots of the Significant Associations between the Expression of Five lncRNAs and Clinical Features of Breast Cancer

Each square indicates a study, and the area of squares is proportional to the weight of the study. The diamond represents the pooled OR and 95% CI.

outcome.[17–19] By far, however, no study has evaluated these associations systematically. Therefore, we conducted this systematic review to clarify the present state of knowledge about the correlations between lncRNAs and BC clinicopathology and survival.

RESULTS

Characteristics of Included Studies

A total of 991 articles was identified by mining databases and manual searching, and 732 articles were left after removing duplication. After screening titles and abstracts, 111 full-text articles remained for further assessment, and 41 articles were excluded according to the selection criteria. Finally, 70 articles involving 9,307 patients were included in the review. The main characteristics and quality score of studies included in the meta-analysis are presented in Table 1, and the information on the rest of the studies is shown in Table S1. Most of these articles were published within the last 3 years. Among all these articles, 63 articles involving 48 lncRNAs described the clinicopathological features of BC, and 48 articles involving 32 lncRNAs investigated the survival of BC.

Association of lncRNA Expression with Clinicopathological Features of BC

Ten lncRNAs, *MALAT1*, *MEG3*, *CCAT2*, *BCAR*, *TUSC7*, *TP73-AS1*, *NEAT1*, *TUG1*, *HOTAIR*, and *CRNDE*, were included in meta-analyses for clinicopathological features.[20–46] Pooled results are presented in Table S2, and the significant associations are shown in Figure 1. We observed that an upregulated *MALAT1* expression level was related to positive progesterone receptor (PR) status (odds ratio

Table 2. Summary of lncRNAs Related to Clinicopathological Features of Breast Cancer

Clinicopathological Feature	lncRNA
Tumor size	SNHG12, HOTTIP, H19, CRNDE, SPRY4-IT1, FGF14-AS2, APOC1P1-3, EGOT, 91H, HOXA-AS2, PVT1, CRALA, SNHG15, SUMO1P3, ARA
LN metastasis	NEAT1, SNHG12, HOTTIP, CCAT1, AFAP1-AS1, Z38, TUNAR, FGF14-AS2, HULC, EGOT, 91H, HIF1A-AS2, UCA1, linc-ROR, HOXA-AS2, GAS6-AS1, linc-ITGB1, DANCR, PVT1, OR3A4, CRALA, FENDRR, SNHG15, SUMO1P3
Histological grade	MEG3, CCAT1, TUNAR, EPB41L4A-AS2, HULC, BC040587, GAS6-AS1, DANCR, OR3A4
TNM stage	TP73-AS1, NEAT1, HOTTIP, CCAT1, AFAP1-AS1, ACTA2-AS1, Z38, SPRY4-IT1, FGF14-AS2, EPB41L4A-AS2, HULC, HOXA-AS2, linc-ITGB1, DANCR, PVT1, OR3A4, CRALA, HOXB-AS5, LINP1, SNHG15, SUMO1P3
ER status	BCAR4, H19, LINC00978, EPB41L4A-AS2, CRALA
PR status	MALAT1, H19, EPB41L4A-AS2, CRALA, FENDRR
HER-2 status	TUSC7, 91H, ANRASSF1, OR3A4, FENDRR

LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

[OR] = 1.41, 95% confidence interval [CI]: 1.08–1.84, p = 0.01), and an elevated *TUSC7* level was related to positive HER-2 status (OR = 2.75, 95% CI: 1.06–7.14, p = 0.04). The expression level of *MEG3* was negatively correlated with tumor histological grade (OR = 0.61, 95% CI: 0.41–0.91, p = 0.01). Moreover, increased levels of *NEAT1* and *TP73-AS1* were associated with advanced TNM stage (OR = 3.52, 95% CI: 1.84–6.73 and OR = 5.76, 95% CI: 2.64–12.6, respectively; all p < 0.01).

Among the remaining 38 lncRNAs, 4 lncRNAs (*MVIH*, *SOX2OT*, *PTPRG-AS1*, and *ANRIL*) had no relationship with any clinicopathological features of BC.[47,48] The expression of the other 34 lncRNAs (*HOTTIP*, *CCAT1*, *H19*, *HULC*, etc.) was related to one or more clinical parameters of BC, including tumor size; lymph node metastasis; histological grade; TNM stage; and estrogen receptor (ER), PR, and HER-2 statuses (p < 0.05).[48–79,87] The p values of the correlations between these lncRNAs and BC clinicopathological features are shown in Table S3, and Table 2 summarizes all the lncRNAs that were related to clinicopathological features of BC.

Prognostic Value of lncRNA Expression for BC Survival

Five lncRNAs, including *MALAT1*, *MEG3*, *CCAT2*, *HOTAIR*, and *NEAT1*, were included in meta-analyses for survival.[13,22–31,80–86] As shown in Figure 2, patients with high expression of *CCAT2*, *MALAT1*, or *NEAT1* had shorter overall survival (OS) (hazard ratio [HR] = 1.29, 95% CI: 1.03–1.63, p = 0.03; HR = 2.78, 95% CI: 1.95–3.97, p < 0.01; HR = 1.65, 95% CI: 1.08–2.54, p = 0.02, respectively), while an increased level of *MEG* was associated with better OS (HR = 0.47, 95% CI: 0.37–0.71, p < 0.01). In addition, elevated expression of *CCAT2* or *HOTAIR* was related to poor metastasis-free survival (MFS) (HR = 1.18, 95% CI: 1.02–1.36, p = 0.03; HR = 1.90, 95% CI: 1.41–2.55, p < 0.01, respectively) (Figure 3).

Another 24 lncRNAs were also correlated with OS of BC. Among them, the elevated expression of 7 lncRNAs (*FGF14-AS2*, *AFAP1-AS1*, *EPB41L4A-AS2*, *BC040587*, *EGOT*, *GAS6-AS1*, and *FENDRR*) related to a better survival,[56,59–62,66,87] while increased expression of the 17 other lncRNAs (*BCAR4*, *HOTTIP*, *CCAT1*, *Z38*, *TUNAR*, *CRNDE*, *HULC*, *MVIH*, *TP73-AS1*, *linc-ITGB1*, *PVT1*, *UCA1*, *OR3A4*, *DANCR*, *LINP1*, *SNHG15*, and *SUMO1P3*) related to a worse survival[36,38,46,47,51–55,69,71–73,76–78,88] (Figure 4). The expression of 9 lncRNAs (*MALAT1*, *HOTTIP*, *MVIH*, *LINC00978*, *linc-ITGB1*, *MEG3*, *GAS6-AS1*, *HOTAIR*, and *LINP1*) had an impact on disease-free survival (DFS) of BC. Furthermore, *MALAT1*, *MEG3*, and *HOTAIR* levels had a relationship with relapse-free survival (RFS); *CCAT1*, *MEG3*, and *FENDRR* levels were associated with progression-free survival (PFS); and the expression of *BCAR4* was related to MFS. The detailed information is provided in Table 3.

DISCUSSION

Increasing evidence has demonstrated that lncRNAs are involved in the initiation and progression of cancer and participate in multiple biological behaviors of cancer, including cell proliferation, apoptosis, migration, and metastasis.[12,89] Aberrant expression of lncRNAs has been observed in various types of cancer, including BC.[17,18] Previous reviews and meta-analyses have reported the prognostic values of lncRNAs in multiple cancers, such as colorectal cancer, ovarian cancer, prostate cancer, lung cancer, etc.[90–93] However, no one investigated BC specifically. Since many studies found that dysregulation of multiple lncRNAs may have an impact on the prognosis of BC, we conducted this systematic review to highlight the prognostic values of lncRNAs in BC. To our knowledge, this review is a thorough work that comprehensively clarifies the association of lncRNA expression with clinicopathological features and survival of BC.

In the present study, we systematically reviewed all the published literature regarding the clinical and prognostic values of lncRNAs in BC. We identified a number of relevant lncRNAs, most of which have been studied only once. We found that the expression levels of these lncRNAs were most often linked to tumor size (n = 15), lymph node metastasis (n = 24), and TNM stage (n = 21), while fewer of them associated with histological grade (n = 9), hormone receptor status (n = 9), and HER-2 status (n = 6). Moreover, several lncRNAs were related to more than two clinical features of BC. However, all the lncRNA expression had no relationship with patient age. These results indicated the intrinsic role of lncRNAs in the pathogenesis and progression of BC, which suggested lncRNAs may be important biomarkers for BC. As for survival, most of the studies investigated the relationship between lncRNA expression and OS, and a majority of them (n = 28) had a statistically significant correlation with the OS of BC. Only a few studies evaluated the associations of lncRNA expression with other types of survival, including DFS, MFS, PFS, and RFS, and there was also a strong connection between them. These results revealed the significant prognostic value of lncRNAs

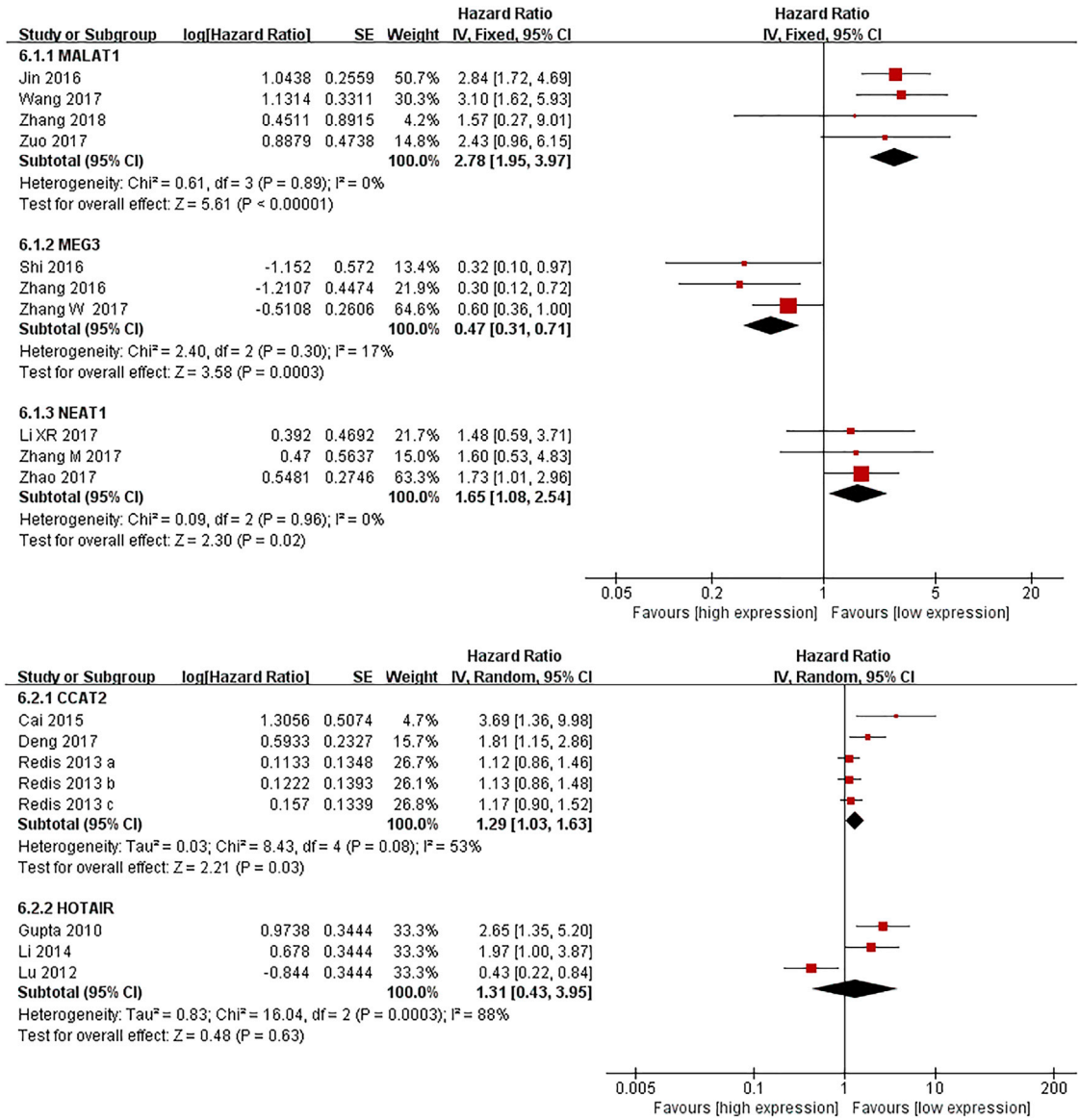

Figure 2. Forest Plots of the Associations between the Expression of Five lncRNAs and Breast Cancer Overall Survival

Each square indicates a study and the area of squares is proportional to the weight of the study. The diamond represents the pooled HR and 95% CI.

in BC. Hence, these lncRNAs may be independent predictors of prognosis in BC.

The most frequently evaluated lncRNAs in BC included *MALAT1*, *MEG3*, *CCAT2*, and *HOTAIR*. All of them are statistically significant predictors of BC prognosis. The expression of *MALAT1*, *CCAT2*, and *HOTAIR* was increased in BC, and the upregulation was associated with shorter survival. The expression of MEG3 was downregulated in BC. Tumor with a lower MEG3 expression tended to be poorly differentiated, and the survival of patients was worse. This indicated the oncogenic role of *MALAT1*, *CCAT2*, and *HOTAIR* in BC, whereas *MEG3* may be a tumor suppressor of BC. In terms of mechanism, *MALAT1* was reported to mainly act as a competing endogenous RNA (ceRNA) to sponge microRNAs, thus regulating cell progression, invasion, and metastasis in BC through their targets.[24–26] *CCAT2* can promote BC tumor growth and metastasis by regulating Wnt- and transforming growth factor β (TGF-β)- signaling pathways.[80,94] *HOTAIR* was proven to promote BC metastasis through inducing or repressing critical genes in cell proliferation and migration as well as modulating the cancer epigenome.[13,95] As for *MEG3*, it can inhibit cell proliferation, invasion, and angiogenesis both by sponging microRNAs and through regulating signaling transduction, such as the AKT and TGF-β pathways.[28,96,97]

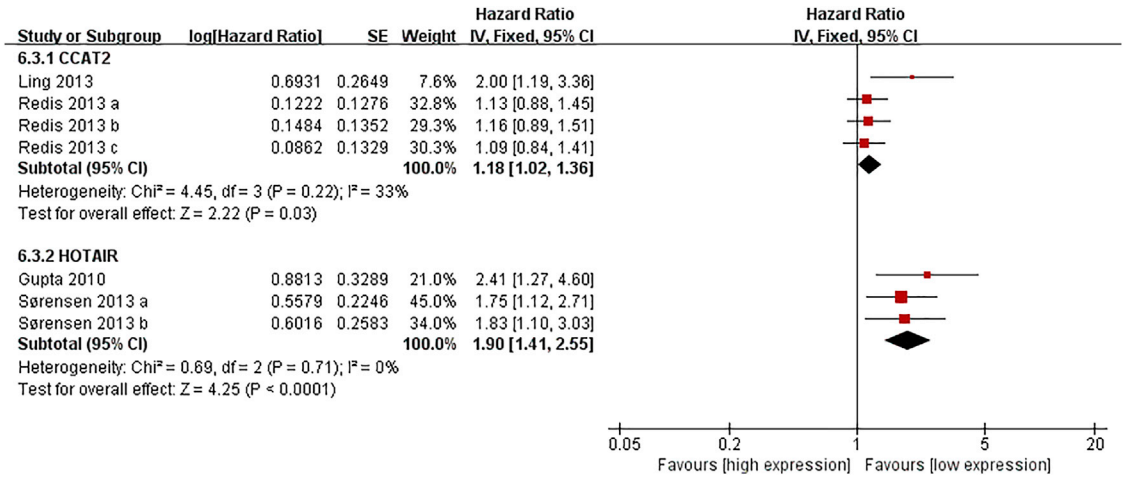

Figure 3. Forest Plots of the Associations between the Expression of Two lncRNAs and Breast Cancer Metastasis-free Survival

Each square indicates a study and the area of squares is proportional to the weight of the study. The diamond represents the pooled HR and 95% CI.

Overall, the results are comprehensive and credible because the quality of included articles is relatively high. However, there are still limitations in our analysis. First, heterogeneity exists between studies regarding the same lncRNA, and the heterogeneity is stubborn owing to the differences in methodology, such as sample selection, tissue preservation, determination of cutoff value, and statistical analysis. Second, almost all the studies in our review reported a statistically significant result. Although the Begg's funnel plot suggested there is no publication bias on OS (Figure S1), we still suspect that selective reporting bias is prominent in the literature regarding lncRNA and BC prognosis. Third, about half of the included studies had a small sample size (<100), and small studies are considered associating with inflated estimates of effect size and higher heterogeneity.[98,99] Lastly, language bias may exist since only two languages were used in the literature review.

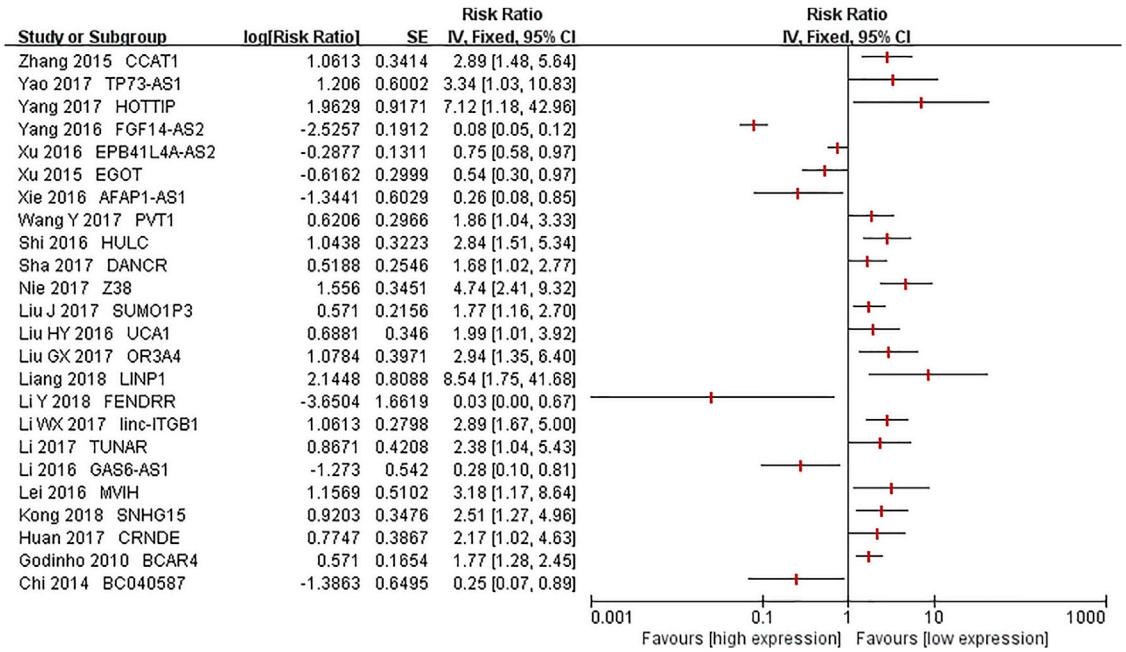

Figure 4. Forest Plots of the Associations between the Expression of lncRNAs and Breast Cancer Overall Survival in Single Studies

Each square indicates a study.

Table 3. Summary of Other Significant Associations of lncRNAs with Breast Cancer Survival

Survival	lncRNA	HR and 95% CI	Analysis	Reference
DFS	MALAT1	2.36 (1.04–5.38)	univariate	23
	HOTTIP	4.08 (1.13–14.71)	multivariate	51
	MVIH	2.55 (1.06–6.12)	multivariate	47
	LINC00978	2.27 (1.24–4.16)	multivariate	63
	linc-ITGB1	3.13 (1.89–6.14)	multivariate	69
	MEG3	0.59 (0.36–0.96)	univariate	28
	GAS6-AS1	0.28 (0.13—0.60)	multivariate	66
	HOTAIR	1.89 (1.15–3.11)	univariate	43
	LINP1	8.40 (1.72–41.06)	univariate	76
RFS	MALAT1	2.02 (1.02–3.98)	multivariate	22
	MEG3	0.37 (0.15–0.87)	multivariate	30
	HOTAIR	0.47 (0.26–0.87)	multivariate	84
PFS	CCAT1	3.59 (2.00–7.84)	multivariate	52
	MEG3	0.37 (0.13–0.88)	multivariate	29
	FENDRR	0.578 (0.454–0.735)	multivariate	87
MFS	BCAR4	1.41 (1.03–1.94)	univariate	36

DFS, disease-free survival; MFS, metastasis-free survival; RFS, relapse-free survival; PFS, progression-free survival.

Our analysis demonstrated the prognostic value of lncRNAs in BC, and it highlighted the important biological function of lncRNAs in BC progression. These lncRNAs may exert their effects by directly binding to functional protein, modulation of DNA methylation, or post-transcriptional regulation of target genes.[89,100,101] These genes and proteins include those that are involved in tumorgenesis and metastasis, such as *Wnt*, *P53*, *PI3K*, *MYC*, etc. Therefore, dysregulation of certain lncRNAs may have an effect on the development of BC, thus influencing the outcome of BC. Though the exact mechanisms are not yet fully clarified, we believe they will be better understood in the future with more studies in this field.

In conclusion, this systematic review identified a number of lncRNAs that were correlated with BC clinicopathological features and survival, and almost all the lncRNAs are statistically significant predictors of BC prognosis. The weightiness of these correlations is difficult to ascertain due to a lot of uncontrollable factors. Hence, a large-scale study with a standardized process of detection, analysis, and report is needed to further verify the prognostic value of these lncRNAs in BC.

MATERIALS AND METHODS

This review has been performed based on preferred reporting items for systematic reviews and meta-analyses (PRISMA).[102]

Search Strategy

The databases of PubMed, Embase, Web of Science, as well as Chinese National Knowledge Infrastructure (CNKI) and Wanfang were systematically searched to identify all the eligible literature up to April 13, 2018. The following keywords and search terms were used: long noncoding RNA or long ncRNA or lncRNA or lincRNA or long intergenic non-coding RNA or long untranslated RNA, BC or breast carcinoma or breast tumor or breast neoplasm, and clinical or clinicopathological or clinicopathology or survival or odds ratio or OR or hazard ratio or HR. Additionally, references in relevant articles were also screened manually. The languages of the retrieved literature were confined to English and Chinese.

Inclusion and Exclusion Criteria

Studies were included if they fulfilled the following criteria: (1) original study focus on human beings, (2) investigated the relationship between lncRNA expression and clinicopathological features or survival of BC, (3) reported an OR or HR with 95% CI or there were sufficient data to calculate them, (4) full text was available. Exclusion criteria were as follows: (1) lacked key information, such as clinical parameters and survival curves, or lacked usable data; (2) reprocessed data from public databases; (3) HRs were for a combination of multiple lncRNAs; and (4) reviews, letters, single case reports, and conference abstracts. If multiple articles published by the same author reporting overlapped data, only the most complete one was included. The details about the selection process are shown in Figure 5.

Quality Assessment and Data Extraction

Two authors (T.T. and M.W.) reviewed potentially eligible articles independently. The Newcastle-Ottawa Scale was used to assess the quality of each study.[103] The following information was extracted from each included study: (1) basic information including first author's name, publication year, country of origin, names of lncRNAs, sample size, expression levels of lncRNAs in BC, detection methods, sample type, outcome measurements, follow-up duration, cutoff value, and analysis method for survival; (2) p values of the correlation between lncRNA expression and clinicopathological features of BC and the original data for calculating ORs and their 95% CIs; and (3) HRs and their 95% CIs for survival analysis. If HRs were not directly accessible in the text, Kaplan-Meier survival curves were read using Engauge Digitizer (version 4.1) to obtain data. Different datasets for one lncRNA or one dataset concerning several lncRNAs in the same article was considered to be separate studies and the HR was extracted respectively; but, if multiple datasets were combined into a single dataset, we only extracted the pooled HR. Any discrepancy was discussed by all authors to reach a consensus.

Statistical Analysis

ORs and their 95% CIs were used to estimate the association of lncRNAs with clinical features of BC. Patients were divided into two groups for comparison (for instance, histological grade III versus I and II, TNM stages III and IV versus I and II, and ER/PR status positive versus negative). As for survival rates, HRs with corresponding 95% CIs were used. All the ORs and HRs were calculated for high expression of lncRNAs. When two or more different studies investigated the same lncRNA, a meta-analysis was carried out to combine the effect size. The Z test was used to determine the significance of ORs or HRs. Heterogeneity between studies was tested using

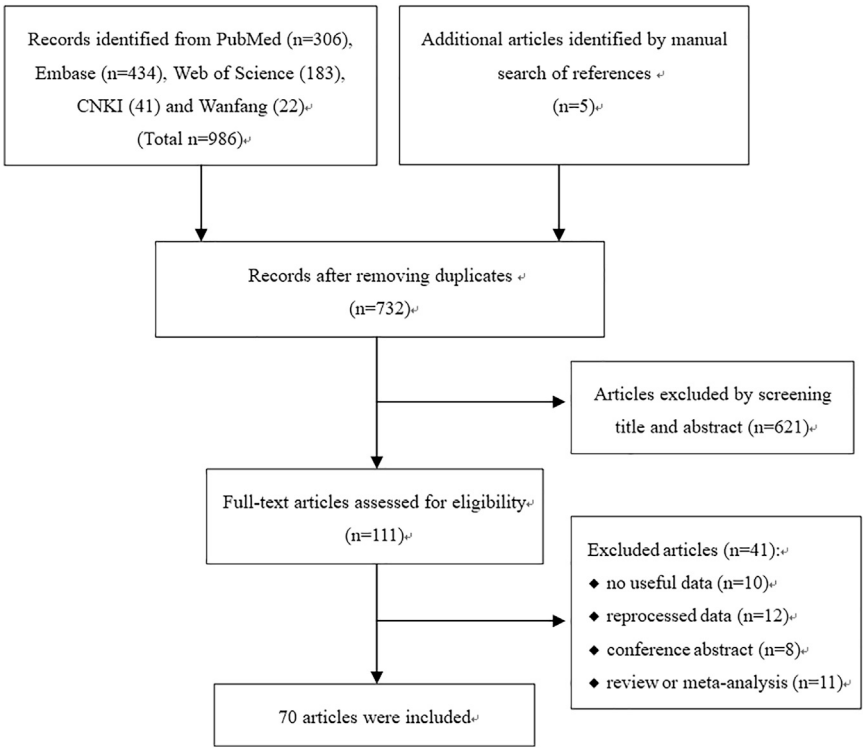

Figure 5. Flow Diagram of the Literature Review Process

A total of 991 articles were found by searching databases. After removing duplication, 732 articles were screened by title and abstract. Then, 111 articles were reviewed for full-text and 70 articles were finally included.

Q statistic and I^2 test. When I^2 value was more than 50%, which indicated a significant heterogeneity, the random-effects model was utilized. Otherwise, the fixed-effects model was used. All statistical analyses were done with the software Review Manager 5.3 (Cochrane Collaboration, London, UK). A p value less than 0.05 was considered statistically significant.

SUPPLEMENTAL INFORMATION

Supplemental Information includes one figure and three tables and can be found with this article online at https://doi.org/10.1016/j.omtn.2018.05.018.

AUTHOR CONTRIBUTIONS

T.T. and Zhijun Dai conceived and designed the study. T.T. and M.W. searched and reviewed literature. S.L., Y.G., Zhiming Dai, K.L., and C.D. contributed to data collection, analysis, and interpretation. P.Y., Y. Zhu, Y. Zheng, and P.X. prepared tables and figures. T.T. drafted the manuscript. Zhijun Dai and W.Z. revised the manuscript. All authors approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no competing interest.

ACKNOWLEDGMENTS

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