Long Non-coding RNAs act as Prognostic Biomarkers in Breast and Gynecologic Cancers

Fan Zhao

Zhejiang University School of Medicine

Huiqi Chen

Zhejiang University School of Medicine

Kelie Chen

Zhejiang University School of Medicine

Shengchao Wang

Zhejiang University School of Medicine

Dexin Yang

Zhejiang University School of Medicine

Honghe Zhang

Zhejiang University School of Medicine

Weiguo Lu

Zhejiang University School of Medicine

Dajing Xia

Zhejiang University School of Medicine

Yihua Wu (✉ georgewu@zju.edu.cn)

Zhejiang University, Hangzhou

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Abstract

Background

It is well-known that long non-coding RNAs (lncRNAs) play essential roles in cancer development and progression. This study aimed to assess the potential prognostic value of specific lncRNAs in breast and gynecologic cancers.

Methods

PubMed, EMBASE, Cochrane library and TCGA databases were systematically searched from inception to January, 2019, and identified according to eligibility criteria. A random-effects model was adopted to calculate combined hazard ratios to explore the association between specific lncRNA expression level and survival in breast and gynecologic cancers. Subgroup and publication bias analyses were also conducted.

Results

111 studies encompassing nearly 20000 participants and 25 lncRNAs were included in the current study. Of the listed lncRNAs, we identified 3 lncRNAs significantly associated with both overall survival (OS) and disease-free survival (DFS) in breast and gynecologic cancers, indicating that they might act as promising prognostic biomarkers in clinical applications. Specifically, HOTAIR and PVT1 had a negative impact on survival outcome, while GAS5 was associated with better prognosis. Further subgroup analyses identified HOTAIR as a biomarker for the poor survival whether in an Asian population or in European and American populations and GAS5 as a biomarker for the relatively good prognosis of both breast and gynecologic cancers.

Conclusions

We here highlight that abnormal expression of 3 lncRNAs, including HOTAIR, GAS5, PVT1 might significantly affect the survival of breast and gynecologic cancer patients and serve as novel prognostic biomarkers for breast and gynecologic cancers.

Introduction

Breast and gynecologic cancers, including breast cancer, ovarian cancer, endometrial cancer and cervical cancer, are the major malignant tumors in women worldwide and seriously endanger the health of women, which account for nearly 40% of cancer risk and 30% of cancer mortality for women [1]. As estrogen associated tumors, it is widely accepted that breast cancer and gynecologic cancers share several similar risk factors and genetic characteristics [2, 3]. Besides, the prognosis of breast and gynecologic cancers is still not optimistic owing to the distinctive properties of easy metastasis [4, 5].

Recent genome sequencing studies have shown that the human genome consists of less than 2% protein-coding genes, and more than 90% of genome is transcribed into non-coding RNAs [6, 7]. Long non-coding RNAs (lncRNAs) are defined as transcripts greater than 200 nucleotides in length without protein encoding

potential [8]. Although lncRNAs are incapable of encoding proteins, it can regulate gene expression at various levels, such as transcriptional regulation, post-transcription regulation and epigenetic mode [9, 10]. Nowadays, an increasing number of lncRNAs have been identified due to the development of high-throughput sequencing.

Interestingly, plenty of lncRNAs were only expressed in differentiated tissues or specific cancer types [11]. Previous studies demonstrated the participants of lncRNAs in different types of human cancers with both oncogenic and tumor repressive effects. And their enrichment, conserved sequences, and altered expression have been observed in breast and ovarian cancers [12]. It was proposed that lncRNAs could target chromatin modification complexes or RNA binding proteins to alter gene expressing programs which exhibited distinct gene expression patterns in primary tumors and metastases [13]. In addition, available studies have recognized the considerable role of lncRNAs in various stages of carcinogenesis and metastasis [14]. And metastasis was the most important biological behavior of tumor development and progression and closely related to cancer prognosis. Therefore, specific lncRNAs might be explored as potential prognostic biomarkers for breast and gynecologic cancers.

Several studies have evaluated the association between tissue lncRNA expression and breast and gynecologic cancers but the results did not reach a consensus with each other. For instance, Gupta et al. demonstrated that HOTAIR was increased in expression in primary tumors and metastases in breast cancer [15]. However, Lu et al. found that HOTAIR globally induced repressive chromatin status by promoting the formation of H3K27me3, suggesting that HOTAIR might act as a tumor suppressor under certain conditions [16]. Zhang et al. proposed that low expression of MEG3 was likely to be related to promoter hypermethylation in cervical cancer [17]. Cao et al. reported that CCAT1 was upregulated in epithelial ovarian cancer (EOC) tissues, and significantly associated with FIGO stage, histological grade and poorer survival of EOC patients [18]. Besides, it was shown that MALAT1 was downregulated in breast cancer tissue, and knockdown of MALAT1 in breast cancer cell lines induced epithelial-mesenchymal transition (EMT) via phosphatidylinositol-3 kinase-AKT pathways [19]. However, few studies have systematically assessed the role of lncRNAs in breast and gynecologic cancers. Thus, the aim of this study was to identify promising lncRNAs as biomarkers for breast and gynecologic cancers with a literature search and data extracted from The Cancer Genome Atlas (TCGA) database and offer an overview for further studies.

Methods

Literature search and study selection

The literature searches were performed in PubMed, EMBASE and Cochrane library (up to January, 2019) for eligible studies. The search terms were shown as follows: ("lncRNA" or "Long ncRNA" or "Long Non-Translated RNA" or "Long Non-Coding RNA" or "Long Non Coding RNA" or "Long Non-Protein-Coding RNA" or "Long Non Protein Coding RNA" or "Long Noncoding RNA" or "Long Untranslated RNA" or "Long ncRNAs" or "Long Intergenic Non-Protein Coding RNA" or "Long Intergenic Non Protein Coding RNA" or

“LincRNAs” or “LINC RNA”) AND (“Ovarian neoplasm” or “Ovarian cancer” or “Ovarian tumor” or “Ovarian tumour” or “Ovarian carcinoma” or “Ovarian malignancy” or “Endometrial neoplasm” or “Endometrial cancer” or “Endometrial tumor” or “Endometrial tumour” or “Endometrial carcinoma” or “Endometrial malignancy” or “Cervical neoplasm” or “Cervical cancer” or “Cervical tumor” or “Cervical tumour” or “Cervical carcinoma” or “Cervical malignancy” or “Breast neoplasm” or “Breast cancer” or “Breast tumor” or “Breast tumour” or “Breast carcinoma” or “Breast malignancy”). After excluding duplicates, titles and abstracts were scanned for potential eligible studies. The full articles of remaining studies were carefully reviewed to determine whether the inclusion criteria were met. In order to make the results more convincing, TCGA datasets were also applied to conduct the meta-analysis. This study was designed, conducted and reported according to PRISMA and MOOSE statements [20, 21].

The pertinent studies were selected if they meet the following criteria: (1) Studies described the association between tissue lncRNA expression level and prognosis or clinicopathological features of breast and gynecologic cancers; (2) Clinicopathological features or Hazard ratio (HR) estimates with the corresponding 95% confidence intervals (CIs) for overall survival (OS), disease-free survival (DFS) were available or could be calculated; (3) The number of the studies which reported the association between expression level of a certain lncRNA and prognosis of breast and gynecologic cancer patients must be greater than or equal to 3 (including TCGA datasets). (4) Articles were eligible for evaluation as full English papers. Reviews, letters, meeting abstracts, notes or comments were excluded. The studies concentrating on circulating lncRNAs were also excluded in our studies. Besides, to avoid overlapping data, we excluded the studies reporting the survival outcome with data extracted from TCGA database.

Data extraction and quality assessment

The data from each study were independently evaluated and extracted by 2 investigators (Fan Zhao and Huiqi Chen). We collected the available information from each study as follows: author, year of publication, country of origin, total number of participants, cancer types, date of inception, follow-up period, type of specimens, detection method, HR, and corresponding 95% CI. And we also extracted the data of clinicopathological parameters if available. HRs from multivariable analysis were first considered in our study due to their adjustment for confounding factors. If a study reported only Kaplan–Meier curves, the survival data were extracted with Engauge Digitizer version 10.6.

The quality assessment of each study was conducted according to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guideline [22]. The total score ranges from 0 to 20, and a higher score represents higher quality.

Data synthesis and statistical analysis

The primary meta-analyses were conducted to identify specific lncRNAs significantly associated with survival of patients with breast and gynecologic cancers. Chi-square and I^2 test were applied to assess the

heterogeneity among studies. $P \leq 0.10$ and/or $I^2 > 50\%$ suggests significant heterogeneity [23]. Combined HRs or ORs and 95% CIs were calculated using the DerSimonian-Laird random-effects methods [24]. The significance of the pooled HRs or ORs were determined by Z test ($p < 0.05$ was considered significant). Subgroup analyses were adopted to evaluate potential modifying effect of variables and explore the source of heterogeneity in term of ethnic populations and cancer types. Funnel plots were constructed to assess the potential publication bias. All analyses were conducted using Stata software (version 12.0; StatCorp, College Station, TX, USA).

Results

Study characteristics and data quality

After searching PubMed, EMBASE and Cochrane library, a total of 3748 articles were retrieved. And 2632 articles were assessed after removing 839 duplicated records. Then, titles and abstracts were scanned, after which, 277 remaining articles entered the process of full-text reading. 165 articles were excluded for following reasons: insufficient data ($n=32$), foreign language ($n=4$), review article ($n=18$), meeting abstract ($n=5$), limited number of studies which focused on a certain lncRNA ($n=108$). After the above screening process, we identified 110 studies with 25 specific lncRNAs which might play an important part in the development of breast and gynecologic cancers. Afterwards, we extracted data of breast and gynecologic cancers from TCGA datasets according to the type of lncRNAs.

Finally, 111 eligible studies covering 25 lncRNAs associated with survival outcome or clinicopathological features of breast and gynecologic cancer patients were included in our meta-analysis (including TCGA datasets). The process of screening was shown in Fig. S1, and the characteristics of included studies were shown in Additional file 1. The results of quality assessment were shown in Additional file 2 in accordance with REMARK guideline.

Association between specific tissue lncRNA expression and prognostic outcome in breast and gynecologic cancers

Based on literature screening, we identified 25 specific lncRNAs which might be crucial in the development of breast and gynecologic cancers. And we conducted meta-analyses which covered nearly 20000 patients to systematically evaluate the association between specific lncRNA expression and prognostic outcome of breast and gynecologic cancers, and the results were shown in Fig. 1a and b and Table 1 and Supplementary Table S3 in Additional file 3. Our analyses indicated that 3 lncRNAs (HOTAIR, GAS5, PVT1) might act as promising prognosis biomarkers for breast and gynecologic cancers, because they significantly associated with both OS and DFS for breast and gynecologic cancer patients.

More concretely, higher tissue HOTAIR expression was significantly related to poorer OS (pooled HR=1.70, 95%CI: 1.32-2.19) and DFS (pooled HR=2.04, 95%CI: 1.04-4.03) in breast and gynecologic cancers, as shown in Fig. S2a and S2b. Also, there was a significant association between higher tissue PVT1

expression and poorer OS (pooled HR=1.47, 95%CI: 1.17-1.86) and DFS (pooled HR=1.74, 95%CI: 1.08-2.82) in breast and gynecologic cancers (Fig. S3a and S3b). Similarly, higher tissue SPRY4-IT1, HOXA11-AS, LINP1 and SNHG15 expression might result in poorer OS and DFS in breast and gynecologic cancers (Supplementary Table S3 in Additional file 3), but this conclusion still remained unclear due to the limited study numbers.

Interestingly, 2983 patients were included to evaluate the association between tissue GAS5 expression and prognostic outcome of breast and gynecologic cancer patients, and the pooled HR was 0.51 (95%CI: 0.34-0.77) for OS and 0.40 (95%CI: 0.25-0.63) for DFS, indicating that higher tissue GAS5 expression level predicted better prognostic outcome in breast and gynecologic cancers (Fig. S4a and S4b).

In addition, there was a significant association between tissue MALAT1 (pooled HR=1.51, 95%CI: 1.09-2.08), NEAT1 (pooled HR=1.80, 95%CI: 1.25-2.58), CCAT2 (pooled HR=1.53, 95%CI: 1.09-2.14) expression and OS rather than DFS in breast and gynecologic cancers, as shown in Table 1. Nevertheless, there was a significant association between tissue UCA1 (HR=3.35, 95%CI: 1.31- 8.56), CRNDE (pooled HR=11.79, 95%CI: 4.29-32.46) expression and DFS rather than OS in breast and gynecologic cancers (Table 1).

Of note, no significant association was found between tissue ANRIL, CCAT1, FEZF1-AS1 and HOTTIP expression and prognostic outcome of breast and gynecologic cancers, indicating that they might not be effective biomarkers for breast and gynecologic cancers in clinical applications (Table1). And another included lncRNAs whose study number was less than 3 were shown in Additional file 1.

Subgroup analyses for the association between specific lncRNA expression and OS in breast and gynecologic cancers

In order to evaluate potential modifying effect of variables and explore the source of heterogeneity, subgroup analyses were conducted according to population and cancer types, which were shown in Fig. 1a, Table 2 and Supplementary Table S4 in Additional file 3. And to make the results of subgroup analyses more convincing, the number of concluded study in each subgroup must be greater than or equal to 2.

Firstly, subgroup analyses were conducted according to population. The analyses indicated that higher tissue HOTAIR expression was significantly associated with poorer OS of breast and gynecologic cancer patients whether in an Asian population (pooled HR=2.05, 95%CI: 1.35-3.11) or in European and American populations (pooled HR=1.49, 95%CI: 1.01-2.20). However, significant association between lncRNAs and survival outcome was uniquely observed in an Asian population for PVT1 (pooled HR=2.07, 95%CI: 1.44-3.00), MALAT1 (pooled HR=2.90, 95%CI: 2.03-4.14) and CCAT2 (pooled HR=2.48, 95%CI: 1.82-3.37).

As for the cancer types, the analyses indicated that higher tissue GAS5 expression was significantly associated with better OS of both breast (pooled HR=0.42, 95%CI: 0.20-0.86) and gynecologic cancer (pooled HR=0.56, 95%CI: 0.34-0.94) patients. Besides, we proposed that higher tissue expression of

HOTAIR (pooled HR=1.98, 95%CI: 1.43-2.74), PVT1 (pooled HR = 1.45, 95%CI: 1.12-1.88) and NEAT1 (pooled HR=1.78, 95%CI: 1.15-2.78) might predicted OS of gynecologic cancer patients. Besides, MALAT1 (pooled HR=1.83, 95%CI: 1.13-2.96) expression was significantly associated with OS in breast cancer, indicating it might act as potential prognostic biomarkers for breast cancer with protective effects. And the subgroup analyses of another included lncRNAs were shown in Supplementary Table S4 in Additional file 3.

In addition, subgroup analyses suggested that heterogeneity was mainly influenced by different populations.

Association between specific lncRNA expression and clinicopathological features in breast and gynecologic cancers

As shown in Table 3, we also explored the association between specific lncRNA expression and clinicopathological features in breast and gynecologic cancers, such as age, FIGO stage, histology grade, lymph node metastasis (LNM), lymphovascular space invasion (LVSI) and tumor size, which might provide clues why some lncRNAs associated with survival outcome of breast and gynecologic cancers. Higher tissue expression of 10 lncRNAs was significantly associated with FIGO Stage (I-II vs III-IV) of breast and gynecologic cancers, including HOTAIR, UCA1, GAS5, ANRIL, PVT1, CCAT1, CCAT2, CRNDE, FEZF1-AS1 and HOTTIP. In addition, there was a significant association between 3 lncRNAs (ANRIL, CCAT1, FEZF1-AS1) and histology grade (G1+G2 vs G3) in breast and gynecologic cancers. And higher tissue expression of HOTAIR, UCA1, GAS5, ANRIL, CCAT1, NEAT1, CRNDE, HOTTIP was all significant associated with LNM of breast and gynecologic cancers. Besides, there was a trend that UCA1 and MALAT1 were correlated with LVSI in breast and gynecologic cancer patients. Furthermore, only CRNDE was significantly related to tumor size of patients with breast and gynecologic cancers. And the subgroup analyses of another included lncRNAs were shown in Supplementary Table S4 in Additional file 3. In general, these results indicated that different lncRNAs might function differently in clinicopathological features in breast and gynecologic cancers, which might influenced their prognostic values.

Publication bias

Funnel plots were shown in Fig. S5. No publication bias was found for the included studies except for the assessment of association between tissue MALAT1 expression and DFS in breast and gynecologic cancers. Nevertheless, it was still difficult to confirm whether the publication bias really existed due to the limited number of studies.

Discussion

Recently, accumulating evidence has demonstrated that lncRNAs performed their vital function in cancer progression and development [25]. Indeed, it was well established that lncRNA expression profile was closely related to clinically relevant cancer subtypes, suggesting its potential ability to predict tumor behavior and disease prognosis [26]. Besides, several cancer-associated lncRNAs were proved to regulate cancer invasion and metastases [27]. However, it was still controversial whether some specific lncRNAs could act as prognostic biomarkers in breast and gynecologic cancers.

In our present study, based on 111 studies and nearly 20000 participants, we performed a meta-analysis to systematically assess the role of some specific lncRNAs in the progression of breast and gynecologic cancers and the feasibility of clinical applications of lncRNA profile. According to our study, we identified 3 lncRNAs (HOTAIR, PVT1, GAS5) significantly associated with both OS and DFS of breast and gynecologic cancer patients. Of note, the results of the subgroup analyses by ethnic populations indicated that PVT1, MALAT1 and CCAT2 were significantly associated with poorer OS in breast and gynecologic cancers in an Asian population, whereas HOTAIR had universal adaptability to predict poorer OS of breast and gynecologic cancer patients in Asian, European and American populations. Further subgroup analyses according to cancer types identified GAS5 as a protective biomarker for the survival of both breast and gynecologic cancers. Besides, 3 gynecologic specific prognostic biomarkers (including HOTAIR, PVT1 and NEAT1) and 1 breast cancer specific prognostic biomarkers (MALAT1) were also proposed according to our analyses.

Increasing number of studies focused on the prognostic value of HOTAIR in breast and gynecologic cancers. Consistent with our findings, HOTAIR expression has been proposed to be related to cancer cell migration and invasiveness [28, 29], which was the key factor for the progression and development of breast and gynecologic cancers. Some studies provided possible mechanisms for higher HOTAIR expression as a negative prognostic factor in breast and gynecologic cancers. It was known that overexpression of HOTAIR was able to stimulate ER signaling, which led to tamoxifen resistance and tumor progression in breast cancer [30]. Besides, HOTAIR could indirectly inhibit miR-7 which reversed the EMT program of breast cancer stem cells by down-regulating the STAT3 signaling pathway [31]. It was also reported that HOTAIR could act as a sponge of miR-206 and regulate CCND1 and CCND2 expression in ovarian cancer [29].

Similarly, PVT1 was also a promising prognostic biomarker for breast and gynecologic under our analyses. Specifically, PVT1 played an essential role in tumor cell proliferation and growth by regulating KLF5/ β -catenin signaling pathway in breast cancer [32]. Consistently, PVT1 knockdown inhibited cell proliferation and promoted apoptosis in breast and ovarian cancer cell lines [33]. It was noteworthy that PVT1/miR-195 axis could regulate the response of cervical cancer cells to paclitaxel [34].

Furthermore, our studies proposed the potential value for SPRY4-IT1, HOXA11-AS, SNHG15, TP73-AS1 to predict poorer survival outcome, but the reliability of the conclusion was limited due to the numbers of included studies. For example, the exact mechanism for SPRY4-IT1 and HOXA11-AS to play oncogenic roles was still unclear. SPRY4-IT1 was demonstrated to be upregulated in breast cancer tissues and suppress proliferation and increase apoptosis of breast cancer cell through targeting ZNF703 [35]. SPRY4-

IT1 knockdown might inhibit the proliferation and arrest cell cycle at G0/G1 stage in ovarian cancer cells [36]. And it was shown that HOXA11-AS could increase cell proliferation, invasion and metastasis of breast cancer in vivo and in vitro experiments through regulating EMT program [37]. In general, more studies of high quality were needed to confirm their prognostic value.

Unlike the lncRNAs mentioned above, our study showed higher tissue GAS5 expression might predict better prognosis in breast and gynecologic cancers. Overexpression of GAS5 might enhance the sensitivity of cervical cells to cisplatin through miR-21 by regulating the level of PTEN and the phosphorylation of Akt, thus inhibiting cancer cell migration and invasion [38]. Another study demonstrated that GAS5 could act as a ceRNA for miR-196a-5p, which regulated FOXO1 expression and downstream PI3K/Akt phosphorylation and then promoted the progression of triple-negative breast cancer [39]. Consistently, our study noted that higher tissue GAS5 expression inversely associated with lymph node metastasis in breast and gynecologic cancers, which partly explained its capacity as a prognostic biomarker.

Our studies had some strengths. To our knowledge, it was the first study to systematically evaluate the prognostic value of lncRNA profile in breast and gynecologic cancers. Of note, the study was performed through literature search and data extracted from TCGA database, which contributed to the reliability of the results. In addition, we offered some information about the association between specific lncRNA expression and clinicopathological features in breast and gynecologic cancers, which explain partly the prognostic value of some specific lncRNAs. Finally, the methods of this studies were rigorous and in accordance with guidelines for conducting a meta-analysis.

However, there were also some limitations in the current study. Firstly, though subgroup analyses were conducted, the heterogeneity of the studies for some lncRNA analyses could not be fully explained. Besides, due to the limited number of studies, we could not conduct subgroup analyses for some lncRNAs, thus it was difficult for us to explore the potential modifying effect of ethnic populations and cancer types for some lncRNAs, which increased restrictions on our conclusions. What's more, the criterion of high expression of lncRNAs was not consistent among the included studies. And limited data made it impossible for us to analyze the impact of co-expression of several lncRNAs on the prognostic outcome in breast and gynecologic cancers. Therefore, further high-quality and well-designed studies are warranted to confirm our current findings.

Conclusions

The current study demonstrated that tissue lncRNA expression might associated with survival outcome of breast and gynecologic cancers patients and specific lncRNAs could act as prognostic biomarkers of breast and gynecologic cancers, especially for HOTAIR, PVT1 as poorer prognostic biomarkers and GAS5 as a positive prognostic biomarker.

Abbreviations

lncRNAs: Long non-coding RNAs; OS: Overall survival; DFS: Disease-free survival; EOC: epithelial ovarian cancer; EMT: Epithelial-mesenchymal transition; TCGA: The Cancer Genome Atlas; HR: Hazard ratio; OR: Odds ratio; CI: Confidence intervals; REMARK: Recommendations for Tumor Marker Prognostic Studies guideline; LNM: lymph node metastasis; LVSI: Lymphovascular space invasion

Declarations

Acknowledgements

Not applicable.

Authors' Contributions

YW and DX contributed to conception and design of the study, and had the right to grant on behalf of all authors; FZ, HC and KC contributed to design of the study, data acquisition, analysis and interpretation of the data and drafting the manuscript; DY and SW extracted and analyzed data from TCGA database and provided support of bioinformatics analysis; HZ and WL provided valuable suggestions and polished the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data supporting the conclusions of this article are included in the article and its supplementary information files.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1

Meta-analysis of the association between tissue lncRNA expression and survival outcome in breast and gynecologic cancers.

lncRNA	Study number	No. of participants	Pooled HR (95%CI)	
			OS	DFS
HOTAIR	14	3672	1.70(1.32–2.19)*	2.04(1.04–4.03)*
UCA1	6	2647	1.34(0.98–1.82)	3.35(1.31–8.56)*
GAS5	8	2983	0.51(0.34–0.77)*	0.40(0.25–0.63)*
ANRIL	5	2578	1.32(0.97–1.79)	-
PVT1	9	3281	1.47(1.17–1.86)*	1.74(1.08–2.82)*
MALAT1	10	9892	1.51(1.09–2.08)*	1.11(0.58–2.12)
CCAT1	4	2576	1.21(0.85–1.73)	2.01(0.72–5.62)
NEAT1	6	2789	1.80(1.25–2.58)*	-
CCAT2	5	2817	1.53(1.09–2.14)*	1.78(0.97–3.27)
CRNDE	4	2587	1.08(0.69–1.69)	11.79(4.29–32.46)*
FEZF1-AS1	4	2216	1.42(0.88–2.31)	-
HOTTIP	4	1987	1.62(1.00–2.61)	-
-Could not be calculated.				
*Significant association was indicated, statistical z test: P<0.05.				
HR, hazard risk; CI, confidence interval.				

Table 2

Subgroup analyses for the association between tissue lncRNA expression and OS in breast and gynecologic cancers.

Categories	lncRNA	Classification	Study number	No. of participants	HR (95% CI)	Heterogeneity	
						I ²	P
Population	HOTAIR	Asian population	8	630	2.05(1.35–3.11)*	71.20%	0.001
		European and American populations	5	2878	1.49(1.01–2.20)*	78.20%	0.000
	PVT1	Asian population	3	284	2.07(1.44–3.00)*	67.30%	0.009
		European and American populations	3	2568	1.10(0.91–1.33)	46.60%	0.095
	MALAT1	Asian population	4	297	2.90(2.03–4.14)*	0.00%	0.869
		European and American populations	2	2827	1.06(0.84–1.35)	58.30%	0.048
	CCAT2	Asian population	3	352	2.48(1.82–3.37)*	0.00%	0.734
		European and American populations	2	2465	1.08(0.92–1.27)	0.00%	0.509
	CRNDE	Asian population	2	166	0.86(0.19–3.84)	92.90%	0.000
		European and American populations	2	2524	1.15(0.71–1.87)	80.30%	0.000
Cancer type	HOTAIR	gynecologic cancer	9	1895	1.98(1.43–2.74)*	65.20%	0.002
		breast cancer	5	1613	1.26(0.84–1.91)	76.20%	0.002
	UCA1	gynecologic cancer	4	1438	1.32(0.97–1.80)	51.40%	0.067
*Significant association was indicated, statistical z test: P<0.05.							

	breast cancer	2	1149	1.24(0.50–3.03)	94.10%	0.000
GAS5	gynecologic cancer	5	1631	0.56(0.34–0.94)*	86.10%	0.000
	breast cancer	4	1352	0.42(0.20–0.86)*	82.70%	0.001
ANRIL	gynecologic cancer	4	1446	1.39(0.96–2.01)	72.00%	0.003
	breast cancer	2	1132	1.22(0.51–2.93)	73.80%	0.051
PVT1	gynecologic cancer	7	1992	1.45(1.12–1.88)*	73.60%	0.000
	breast cancer	3	1289	1.58(0.79–3.14)	85.20%	0.001
MALAT1	gynecologic cancer	3	1391	1.31(0.84–2.04)	79.10%	0.001
	breast cancer	4	1733	1.83(1.13–2.96)*	75.10%	0.007
CCAT1	gynecologic cancer	2	1295	1.15(0.82–1.62)	55.50%	0.080
	breast cancer	2	1187	1.41(0.37–5.33)	91.30%	0.001
NEAT1	gynecologic cancer	4	1506	1.78(1.15–2.78)*	82.10%	0.000
	breast cancer	3	1283	1.87(0.82–4.26)	89.50%	0.000
CRNDE	gynecologic cancer	3	1492	1.01(0.57–1.78)	83.40%	0.000
	breast cancer	2	1198	1.37(0.84–2.26)	53.50%	0.142
FEZF1-AS1	gynecologic cancer	3	1091	1.46(0.69–3.10)	83.50%	0.000
	breast cancer	2	1125	1.30(0.90–1.89)	0.00%	0.376
*Significant association was indicated, statistical z test: P<0.05.						

Table 3

The association between tissue lncRNA expression and clinicopathological features in breast and gynecologic cancers.

Pooled OR (95%CI) lncRNAs	Age	FIGO Stage (I-II vs III-IV)	Histology Grade (G1 + G2 vs G3)	Lymph node metastasis (LNM)	Lymphovascular space invasion (LVSI)	Tumor size
HOTAIR	1.10(0.79–1.53)	2.41(1.17–4.94)*	1.45(0.87–2.39)	8.18(4.87–13.74)*	1.43(0.70–2.93)	1.01(0.25–3.99)
UCA1	1.03(0.59–1.80)	2.88(1.60–5.17)*	1.24(0.50–3.10)	3.70(1.98–6.91)*	4.38(1.08–17.68)*	1.19(0.34–4.18)
GAS5	0.96(0.70–1.33)	0.15(0.08–0.31)*	0.81(0.57–1.14)	0.18(0.07–0.48)*	1.40(0.76–2.59)	0.60(0.21–1.70)
ANRIL	0.77(0.46–1.27)	5.43(2.57–11.45)*	2.23(1.24–4.00)*	3.42(1.29–9.04)*	-	2.31(0.98–5.44)
PVT1	0.95(0.67–1.36)	4.02(2.27–7.13)*	1.37(0.72–2.63)	0.90(0.35–2.30)	-	0.93(0.35–2.48)
MALAT1	1.25(0.96–1.63)	10.91(0.49–245.45)	0.97(0.44–2.13)	1.86(0.58–5.95)	3.33(1.43–7.75)*	0.73(0.36–1.46)
CCAT1	0.88(0.47–1.64)	38.50(9.31–159.16)*	4.19(1.56–11.23)*	10.59(3.65–30.73)*	-	1.34(0.56–3.21)
NEAT1	0.93(0.66–1.31)	1.66(0.40–6.84)	2.21(0.42–11.70)	3.11(0.59–16.52)	-	0.84(0.41–1.71)
CCAT2	0.77(0.51–1.16)	3.40(1.93–6.00)*	0.92(0.56–1.53)	1.76(0.32–9.54)	-	0.77(0.46–1.29)
CRNDE	0.71(0.37–1.35)	3.02(1.08–8.44)*	2.08(0.79–5.50)	13.29(3.89–45.41)*	-	2.68(1.42–5.07)*
FEZF1-AS1	1.16(0.68–1.97)	2.73(1.48–5.04)*	2.32(1.30–4.15)*	-	-	0.93(0.53–1.64)

- Could not be calculated.

*Significant association was indicated, statistical z test: $P < 0.05$.

The analysis of FIGO stage only included studies focusing on gynecologic cancers.

OR: odds ratio.

Pooled OR (95%CI) IncRNAs	Age	FIGO Stage (I-II vs III-IV)	Histology Grade (G1 + G2 vs G3)	Lymph node metastasis (LNM)	Lymphovascular space invasion (LVSI)	Tumor size
HOTTIP	1.23(0.72–2.12)	0.22(0.08–0.60)*	1.34(0.52–3.46)	0.32(0.18–0.59)*	-	1.43(0.16–12.51)
~ Could not be calculated.						
*Significant association was indicated, statistical z test: $P < 0.05$.						
The analysis of FIGO stage only included studies focusing on gynecologic cancers.						
OR: odds ratio.						

Supplemental Supplementary tables

Table S1. Characteristics of the included studies.

Table S2. Quality assessment performed according to the REMARK guideline.

Table S3. Meta-analysis of the association between tissue lncRNA expression and survival outcome in breast and gynecologic cancers (The number of included studies was less than or equal to 3).

Table S4. Subgroup analyses for the association between tissue lncRNA expression and OS in breast and gynecologic cancers (The number of included studies was less than or equal to 3).

Table S5. The association between tissue lncRNA expression and clinicopathological features in breast and gynecologic cancers (The number of included studies was less than or equal to 3).

Supplementary figure legends

Fig. S1. Flow diagram of study selection process.

Fig. S2. Association between tissue HOTAIR expression and survival of breast and gynecologic cancers. a Forest plots of the association between tissue HOTAIR expression and OS in breast and gynecologic cancers. b Forest plots of the association between tissue HOTAIR expression and DFS in breast and gynecologic cancers.

Fig. S3. Association between tissue PVT1 expression and survival of breast and gynecologic cancers. a Forest plots of the association between tissue PVT1 expression and OS in breast and gynecologic cancers. b Forest plots of the association between tissue PVT1 expression and DFS in breast and gynecologic cancers.

Fig. S4. Association between tissue GAS5 expression and survival of breast and gynecologic cancers. a Forest plots of the association between tissue GAS5 expression and OS in breast and gynecologic cancers. b Forest plots of the association between tissue GAS5 expression and DFS in breast and gynecologic cancers.

Fig. S5. Funnel plots for the association between tissue lncRNA expression and survival outcome of breast and gynecologic patients in the current study.

Figures

Figure 1

Overview of the association between tissue lncRNA expression and survival in breast and gynecologic cancers. a Dot plot visualization of the association between tissue lncRNA expression and survival outcome in breast and gynecologic cancers. The size of the dot encodes the size of p values, and the color represents logarithmic value of HRs. b Schematic plot showed specific lncRNAs associated with prognosis of patients with breast and gynecologic cancers. The color red and green encodes lncRNAs predicting negative and positive survival outcome, respectively.

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