Original Article

# LncRNA RP11-10E18.7 cooperates with lncRNA RP11-481C4.2 to affect the overall survival of breast cancer patients: a TCGA-based retrospective study

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**Background:** As either oncogenes or tumor suppressor genes, long non-coding RNAs (lncRNAs) have a major role in both tumorigenesis and progression of human cancers, including breast cancer (BC). However, the statistical correlation between the lncRNA-lncRNA interaction and prognosis of BC remains unclear.

**Methods:** We analyzed the fragments per kilobase per million (FPKM) lncRNA expression data in tumor tissue samples from 890 female patients with BC in The Cancer Genome Atlas (TCGA) between May 2021 and October 2022. The Cox proportional hazards model adjusted for age, race, clinical stage, neoadjuvant therapy, estrogen receptor (ER), and progesterone receptor (PR) was adopted to evaluate the lncRNA-lncRNA interaction regarding overall survival (OS) of BC. The multiple comparison was corrected by Bonferroni method.

**Results:** *RP11-10E18.7*×*RP11-481C4.2* was significantly associated with OS of BC patients [hazard ratio $(HR)_{interaction}$ =1.04, 95% confidence interval (CI): 1.03–1.06, $P=3.35\times10^{-9}$]. Then, gene-gene interaction analysis was performed for genes co-expressed with lncRNAs. *FOXA1*×*U2SURP* ($HR_{interaction}$ =1.49, 95% CI: 1.28–1.73, $P=2.16\times10^{-7}$) was found to have a similar interactive pattern to *RP11-10E18.7*×*RP11-481C4.2*. after classifying the patients by intersection (3.47), we observed that the effect of FOXA1 opposite in patients with different U2SURP expression level ($HR_{high\ vs.\ low}$ =0.58, 95% CI: 0.34–0.99, P=0.046 in low expression of U2SURP; $HR_{high\ vs.\ low}$ =1.56, 95% CI: 1.18–2.87, P=0.029 in high expression of U2SURP).

**Conclusions:** Our comprehensive study identified *RP11-10E18.7*×*RP11-481C4.2* as a potential biomarker of BC prognosis. The results play an essential role in the impact of lncRNA-lncRNA interaction on BC survival. Our findings elucidated potential molecular mechanisms of BC progression under complex association patterns and provided potential dynamic and reversible therapeutic targets for BC patients.

**Keywords:** Breast cancer (BC); overall survival (OS); prognosis; long non-coding RNA (lncRNA); human

Submitted Oct 18, 2023. Accepted for publication Nov 07, 2023. Published online Nov 17, 2023.
doi: 10.21037/tcr-23-1941
**View this article at:** https://dx.doi.org/10.21037/tcr-23-1941

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## Introduction

Breast cancer (BC) is one of the leading causes of cancer-related mortality, with approximately 2.3 million new cases (11.7%) per year (1). Despite advances in surgery, chemotherapy, radiotherapy, and neoadjuvant therapy, the mortality rate of BC remains a global challenge (2). In addition, BC also shows a high recurrence rate (3). Due to the pathogenic complexity of BC, many biomarkers have been found, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) (4,5). However, the prognosis is still a complex problem, indicating the possible existence of new prognosis-influencing molecular mechanisms (6).

Long non-coding RNAs (lncRNAs) are a large class of transcripts from non-protein-coding regions and a group of non-coding RNAs (ncRNAs) of size >200 nucleotides in length (7). LncRNAs are involved in diverse biological processes, such as cell cycle, cell growth, proliferation, migration, invasion, and apoptosis (8). In recent years, lncRNAs have emerged as crucial players in cancer, with specific lncRNAs identified as potential biomarkers for prognosis and therapeutic targets in various cancer types, such as liver, lung, and ovarian cancers (9-12). Further, some lncRNAs may serve as prognosis biomarkers in BC (13-15).

Over the years, mounting studies have revealed that the interactive effects of lncRNA-microRNA (miRNA), lncRNA-messenger RNA (mRNA), and lncRNA-miRNA-mRNA are prognostic signatures in predicting the survival of BC patients (16-18). However, a gap in our understanding pertains to the statistical correlation between interactions among lncRNAs themselves and their impact on the overall survival (OS) of BC. To address this gap, we conducted an analysis using data from the Cancer Genome Atlas (TCGA) data to explore the potential clinical significance of interactive effects between two lncRNAs in the context of BC prognosis. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1941/rc).

### Highlight box

**Key findings**

- Our study identified RP11-10E18.7×RP11-481C4.2 and FOXA1×U2SURP interactions as potential biomarkers for breast cancer (BC) prognosis.

**What is known and what is new?**

- Long non-coding RNAs (lncRNAs) have emerged as crucial players in cancer, with specific lncRNAs identified as potential biomarkers for prognosis and therapeutic targets in various cancer types.
- This is the first study of the relationship between lncRNA-lncRNA interaction and the overall survival of BC.

**What is the implication, and what should change now?**

- This study was based on the data from the Cancer Genome Atlas (TCGA), therefore, additional available public databases and further researches are warranted.

## Methods

### *Study populations*

The fragments per kilobase per million (FPKM) of lncRNA expression data and corresponding clinical information of BC were derived from the TCGA database (https://portal.gdc.cancer.gov), which includes different types of BC, such as infiltrating ductal carcinomas and infiltrating lobular carcinomas. LncRNA annotation information came from gencode.v22 (https://www.gencodegenes.org/). The study sample was collected between May 2021 and October 2022. The requirement for approval from our Ethics Committee was waived since the study data was acquired from TCGA. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Quality control (QC) procedures for lncRNA expression data*

FPKM data and gencode.v22 annotations were matched to obtain the expression of 15,900 lncRNAs. In order to obtain reliable biomarkers in lncRNA expression data, we performed QC, after which we performed statistical association analysis. The exclusion criteria of lncRNAs were when all gene expression values equaled to 0 or the proportion of missing values was greater than 10%. Further, samples with any missing clinical variables and male patients were also removed. Finally, 890 female samples with 4,636 lncRNAs remained in the subsequent statistical association analysis. LncRNA was logarithmically transformed before analysis. The average age was 57.86 years for patients (*Table 1*). The validation sample was enrolled by the same method, including 157 female samples with 817 lncRNAs.

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**Table 1** Demographic and clinical description of breast cancer patients

| Variable | Overall (N=890) | Alive (N=770) | Dead (N=120) | Validation (N=157) |
|---|---|---|---|---|
| Age (years), mean ± SD | 57.86±13.04 | 57.33±12.68 | 61.27±14.78 | 60.06±11.52 |
| Race, n (%) | | | | |
| Asian | 56 (6.29) | 53 (6.88) | 3 (2.50) | 34 (21.66) |
| Black | 169 (18.99) | 143 (18.57) | 26 (21.67) | 56 (35.67) |
| White | 665 (74.72) | 574 (74.55) | 91 (75.83) | 67 (42.68) |
| Neoadjuvant therapy, n (%) | | | | |
| No | 882 (99.10) | 765 (99.35) | 117 (97.50) | 154 (98.09) |
| Yes | 8 (0.90) | 5 (0.65) | 3 (2.50) | 3 (0.19) |
| Clinical stage, n (%) | | | | |
| I | 164 (18.43) | 149 (19.35) | 15 (12.50) | 25 (15.92) |
| II | 509 (57.19) | 455 (59.09) | 54 (45.00) | 80 (50.96) |
| III | 204 (22.92) | 164 (21.30) | 40 (33.33) | 48 (30.57) |
| IV | 13 (1.46) | 2 (0.26) | 11 (9.17) | 4 (2.55) |
| Histology, n (%) | | | | |
| Infiltrating ductal carcinoma | 625 (70.23) | 540 (70.13) | 85 (70.83) | 118 (75.16) |
| Infiltrating lobular carcinoma | 175 (19.66) | 157 (20.39) | 18 (15.00) | 18 (11.46) |
| Other | 90 (10.11) | 73 (9.48) | 17 (14.17) | 21 (13.38) |
| ER, n (%) | | | | |
| Negative | 211 (23.71) | 175 (22.73) | 36 (30.00) | 44 (28.03) |
| Positive | 679 (76.29) | 595 (77.27) | 84 (70.00) | 113 (71.97) |
| PR, n (%) | | | | |
| Negative | 299 (33.60) | 252 (32.73) | 47 (39.17) | 67 (42.68) |
| Positive | 591 (66.40) | 518 (67.27) | 73 (60.83) | 90 (57.32) |
| HER2, n (%) | | | | |
| Negative | 470 (78.86) | 421 (79.73) | 49 (72.06) | 117 (74.52) |
| Positive | 126 (21.14) | 107 (20.27) | 19 (27.94) | 31 (19.75) |
| Unknown | 294 (33.03) | 242 (43.12) | 52 (43.33) | 9 (5.73) |
| Subtype, n (%) | | | | |
| Basal-like ($ER^-$ & $PR^-$, $HER2^-$) | 102 (17.11) | 87 (16.48) | 15 (22.06) | 28 (17.83) |
| $HER2^+$ ($ER^-$ & $PR^-$, $HER2^+$) | 32 (5.38) | 26 (4.92) | 6 (8.82) | 11 (7.01) |
| Luminal A ($ER^+$/$PR^+$, $HER2^-$) | 368 (61.74) | 334 (63.26) | 34 (50.00) | 89 (56.69) |
| Luminal B ($ER^+$/$PR^+$, $HER2^+$) | 94 (15.77) | 81 (15.34) | 13 (19.12) | 20 (12.74) |
| Unknown | 294 (33.03) | 242 (43.12) | 52 (43.33) | 9 (5.73) |
| Survival year | | | | |
| Median (95% CI) | 2.41 (2.09–2.75) | | | 2.52 (2.18–2.92) |
| Censoring rate, n (%) | 120 (13.48) | | | 20 (12.74) |

SD, standard deviation; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CI, confidence interval.

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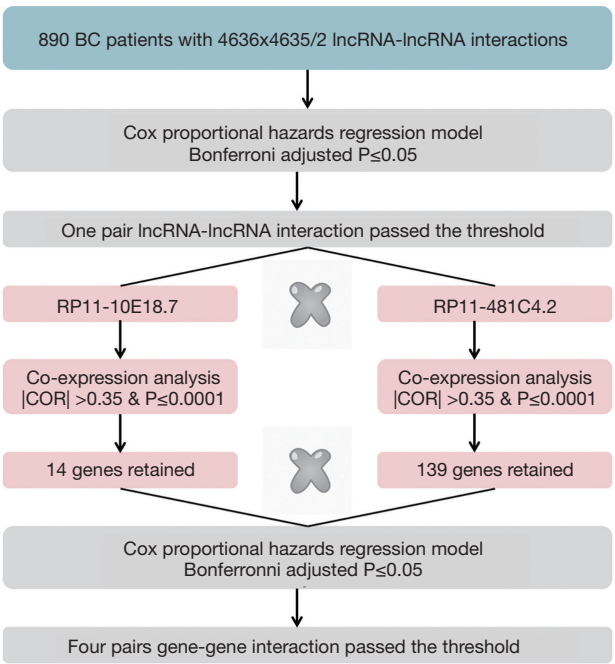


**Figure 1** Flow chart of study design and statistical analyses. R version 3.6.1 was used for creation of the figure. BC, breast cancer; lncRNA, long non-coding RNA.

### *mRNA expression data*

Expression and mRNA sequencing data for all 890 patients were also downloaded from TCGA. Gene expression was measured by RNA sequencing (RNA-seq). Data processing and QC were completed by the TCGA workgroup. RNA-Seq expectation maximization (RSEM) was adopted to normalize raw counts. We downloaded the Level-3 (gene-level) gene quantification data from TCGA and further checked the data quality. Gene expression data were extracted and transformed on $\log_2$ scale before statistical association analysis.

### *Genome-wide lncRNA-lncRNA interaction analysis*

The analysis workflow is displayed in *Figure 1*. We applied a multivariate Cox proportional hazards model adjusted for age, race, clinical stage, neoadjuvant therapy, ER, and PR to test lncRNA-lncRNA interaction items, by using the R package survival (https://cran.r-project.org/web/packages/survival/index.html). The effect size was measure by hazard ratio (HR) and its 95% confidence interval (CI) according to per 5% expression increment. The significance level accounting for multiple comparison was set based on the Bonferroni method, where the significance level was defined as 0.05 divided by the number of tests. Therefore, we controlled the overall type I error at the 0.05 level. The significance level of lncRNA-lncRNA interaction study was set to be $4.65\times10^{-9}$=0.05/(4,636×4,635/2).

### *Gene-gene interaction analysis*

For a better exploration of the function of the significant lncRNA-lncRNA items, the related mRNAs were identified by co-expression methods based on the Pearson correlation, respectively. The related mRNAs were screened according to |COR| >0.35, Bonferroni adjusted P<0.0001. For the significant co-expression genes, we also applied a multivariate Cox proportional hazards model adjusted for the aforementioned covariates to test gene-gene interactions.

### *Statistical analysis*

Continuous variables were described as mean ± standard deviation and compared by Student's *t*-test using R package *t*-test (19), and these categorized variables were summarized as frequency (*n*) and proportion (%) and compared by chi-square test. All statistical analyses were performed using R version 3.6.1 (The R Foundation for Statistical Computing,

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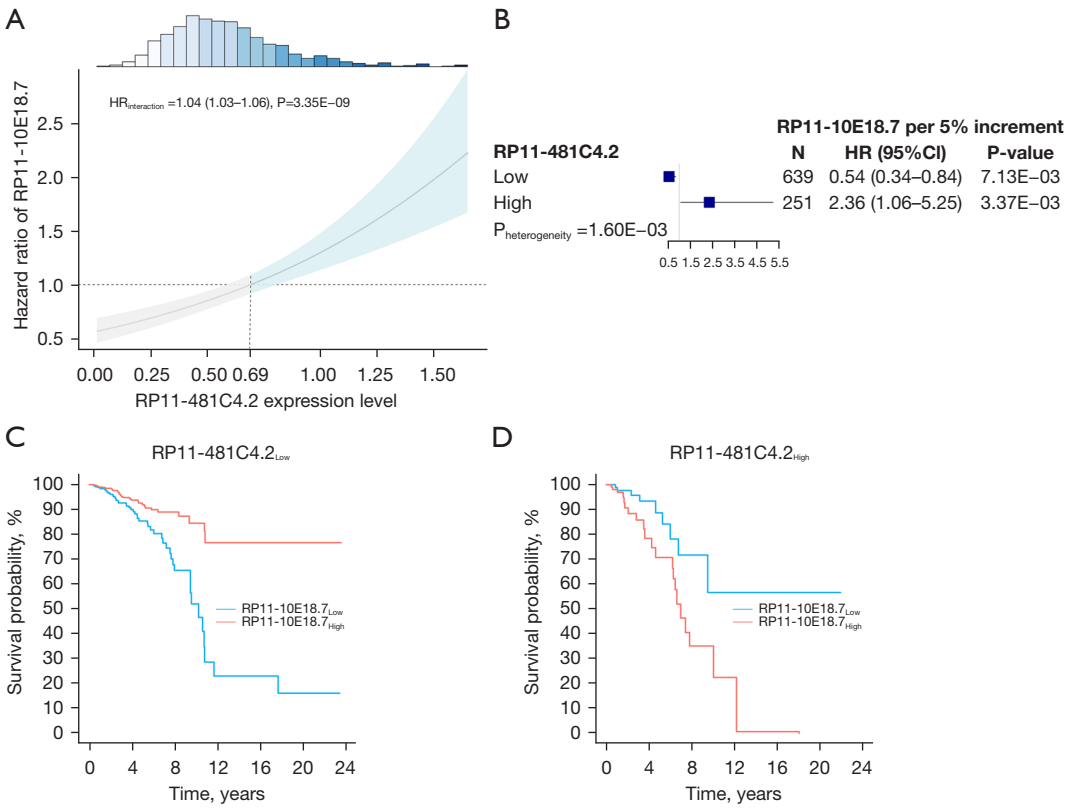


**Figure 2** RP11-10E18.7 and RP11-481C4.2 interaction on overall survival of BC patients. (A) HR of RP11-10E18.7 estimated based on the expression level of RP11-481C4.2. The shallow area represents 95% CI, with grey and blue areas indicating low and high expression, respectively. Histogram on the top shows the distribution of RP11-481C4.2 expression. (B) Forest plots of the effects of RP11-10E18.7 among BC patients with low or high expression of RP11-481C4.2. $P_{heterogeneity}$ was used to evaluate the heterogeneity of HRs across groups. (C) Kaplan-Meier survival curves of low and (D) high expression of RP11-10E18.7 among BC patients with varying RP11-481C4.2 expression levels. R version 3.6.1 was used for creation of the figure. HR, hazard ratio; CI, confidence interval; BC, breast cancer.

Vienna, Austria), unless otherwise specified. P values less than 0.5 were considered as statistically significance.

## Results

For the lncRNA-lncRNA interaction analysis, only *RP11-10E18.7*×*RP11-481C4.2* ($HR_{interaction}$ =1.04, 95% CI: 1.03–1.06, P=3.35×10$^{-9}$) was significantly associated with BC OS. As presented in *Figure 2A*, with the increased expression level of *RP11-481C4.2*, there was the elevated risk for *RP11-10E18.7* on BC OS. Therefore, *RP11-481C4.2* was a modifier of the association between *RP11-10E18.7* and BC survival. To illustrate the modification effect, patients were categorized into low and high groups based on the intersection (0.69) of *RP11-481C4.2* expression in *Figure 2A*. The effect of *RP11-10E18.7* varied across patients with different *RP11-481C4.2* expressions. For patients with a low level of *RP11-481C4.2*, high expression of *RP11-10E18.7* had significantly better OS ($HR_{high\ vs.\ low}$ =0.54, 95% CI: 0.34–0.84, P=7.13×10$^{-3}$) (*Figure 2B,2C*). Conversely, high expression of *RP11-10E18.7* had poor effect on patients with high level of *RP11-481C4.2* ($HR_{high\ vs.\ low}$ =2.36, 95% CI: 1.06–5.25, P=3.37×10$^{-3}$) (*Figure 2B,2D*). The results showed that the effect direction of *RP11-10E18.7* on BC OS was opposite at the low and high levels of *RP11-481C4.2*. To further evaluate our findings regarding *RP11-10E18.7* and *RP11-481C4.2*, we repeated the interaction analysis in the validation dataset of 817 gene expression samples, and the results were similar ($HR_{interaction}$ =1.02, 95% CI: 1.01–1.05, P=3.01×10$^{-9}$).

Based on the BC-related mRNA expression data from TCGA, co-expression analysis was performed on *RP11-*

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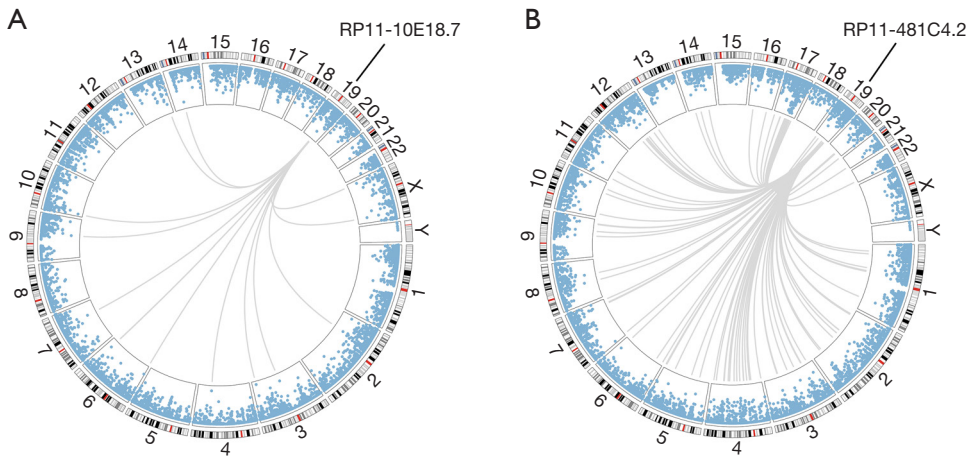


**Figure 3** Co-expression analysis of BC patients from TCGA cohort. (A) RP11-10E18.7 related mRNAs. (B) RP11-481C4.2 related mRNAs. Blue points represent P values of correlation between gene expression and lncRNA, ordered by genomic position. Grey lines represent significant connections with |COR| >0.35 and Bonferroni adjusted P≤0.05. R version 3.6.1 was used for creation of the figure. BC, breast cancer; TCGA, The Cancer Genome Atlas; mRNA, messenger RNA; lncRNA, long non-coding RNA.

**Table 2** LncRNAs associated mRNAs with significant interaction effects

| Interaction | HR (95% CI) | Z | P value | P adjust |
|---|---|---|---|---|
| FOXA1×U2SURP | 1.49 (1.28–1.73) | 5.185 | $2.16\times10^{-7}$ | $4.20\times10^{-4}$ |
| FOXA1×TMEM194A | 1.35 (1.19–1.52) | 4.850 | $1.24\times10^{-6}$ | $2.40\times10^{-3}$ |
| GATA3×U2SURP | 1.41 (1.21–1.64) | 4.410 | $1.04\times10^{-5}$ | 0.020 |
| ESR1×U2SURP | 1.45 (1.23–1.72) | 4.368 | $1.25\times10^{-5}$ | 0.024 |

LncRNA, long non-coding RNA; HR, hazard ratio; CI, confidence interval.

*10E18.7* and *RP11-481C4.2* respectively. The results showed that 14 and 139 genes were closely related to the 2 lncRNAs, respectively, that were then used for gene-gene interaction analysis (*Figure 3*). Finally, 4 pairs of genes were identified with Bonferroni adjusted P≤0.05 (*Table 2*). However, as shown in *Figure 4*, there were high correlations among the expression of these genes, and the subsequent analysis focused on the *FOXA1×U2SURP* that had the lowest P value ($HR_{interaction}$ =1.49, 95% CI: 1.28–1.73, P=$2.16\times10^{-7}$). The associations between *RP11-10E18.7* and *FOXA1* (r=–0.37, P=$3.70\times10^{-30}$), *RP11-481C4.2* and *U2SURP* (r=0.38, P=$1.37\times10^{-32}$) were all significant (Figure S1).

The similar interactive pattern was exhibited between *FOXA1* and *U2SURP* (*Figure 5*). *FOXA1* had an elevated risk on BC OS with the increased expression level of *U2SURP* (*Figure 5A*). Again, after classifying the patients by intersection (3.47), we observed that the effect of *FOXA1* opposite in patients with different *U2SURP* expression level ($HR_{high\ vs.\ low}$ =0.58, 95% CI: 0.34–0.99, P=0.046 in low expression of *U2SURP*; $HR_{high\ vs.\ low}$ =1.56, 95% CI: 1.18–2.87, P=0.029 in high expression of *U2SURP*) (*Figure 5B-5D*).

## Discussion

In this study, we used transcriptional data from TCGA to identify *RP11-10E18.7×RP11-481C4.2* interaction that had an impact on BC OS. Then, through co-expression analysis, 4 pairs of gene-gene interactions, including *FOXA1×U2SURP*, were also found to be associated with BC OS.

Approximately 93% of DNA can be transcribed as RNA in the human genome, 98% of which is known as ncRNAs (20). Among them, lncRNAs are RNAs longer than 200 nucleotides in length that have been demonstrated to play important roles in epigenetic control and the regulation of transcription and translation (21). As a new type of gene regulator, lncRNA is related to the

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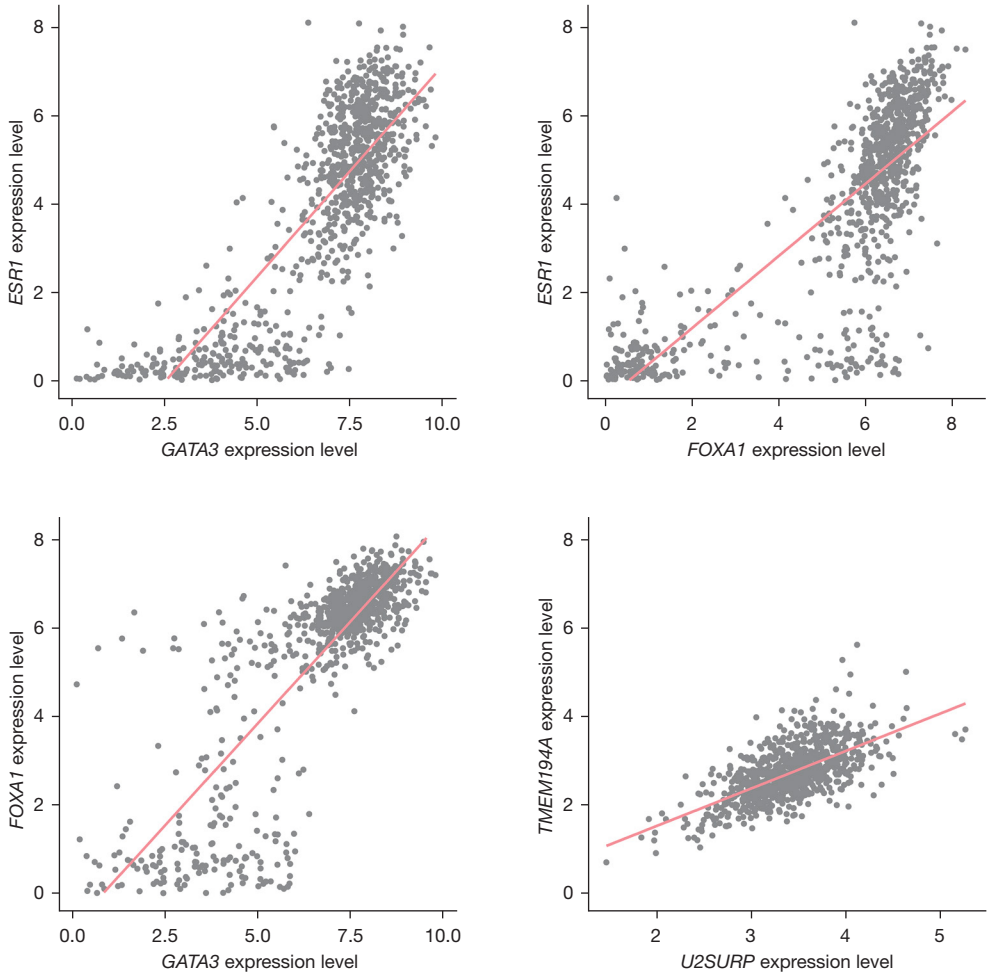


**Figure 4** Correlations among the expression of genes from significant gene-gene interactions. R version 3.6.1 was used for creation of the figure.

occurrence, development, and prognosis of human diseases, especially cancer (22,23). In recent years, lncRNAs have been demonstrated to be engaged in BC development, progression, invasion, and metastasis (24-27).

Several studies have demonstrated that the abnormal expression of some lncRNAs may be associated with the poor prognosis of BC by testing their main effects (28,29). To the best of our knowledge, this may be the first attempt to explore the relationship between lncRNA-lncRNA interactions and BC OS at the population level. Interactions have been shown to provide important clues to the biologic mechanisms of complex diseases (30). Besides this, interactions could increase the power to detect associations and then be leveraged for the identification of new biomarkers (31). Previous studies have identified some gene-gene interactions related to BC survival (32,33). Our results found that biomarkers with *RP11-10E18.7*×*RP11-481C4.2* interaction and *FOXA1*×*U2SURP* interaction significantly affected the prognosis of BC.

LncRNA *RP11-10E18.7* was found to be associated with miRNA hsa-miR-181a-5p that regulated gene *SRPK2* in blood (34). Forkhead box A1 (*FOXA1*) is a forkhead box transcription factor expressed in mammary luminal epithelial cells (LECs) (35). *FOXA1* mutations are a hallmark of ER$^+$ BC and have been widely regarded as a determinant of breast tumor response to endocrine therapy as well as a marker for favorable patient prognosis (36). Previous study has indicated that elevated *FOXA1* expression level is associated with better outcome in BC (37). However, our results showed that high level of *FOXA1* expression had protective effect on BC survival only when *U2SURP* expression was low, meaning that *U2SURP* modified the relationship between *FOXA1*

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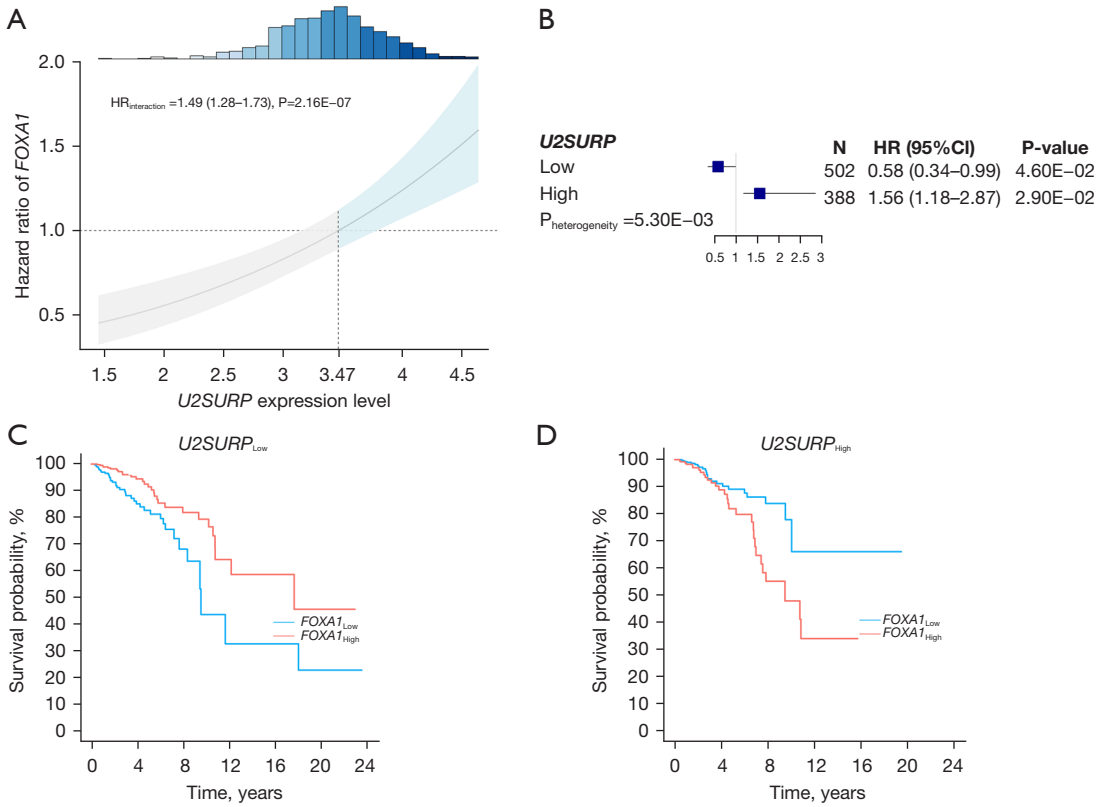


**Figure 5** *FOXA1* and *U2SURP* interaction on survival of BC patients. (A) HR of *FOXA1* estimated based on the expression level of *U2SURP*. The shallow area represents 95% CI, with gray and blue areas indicating low and high expression, respectively. Histogram on the top shows the distribution of *U2SURP* expression. (B) Forest plots of the effects of *FOXA1* among BC patients with low or high expression of *U2SURP*. $P_{heterogeneity}$ was used to evaluate heterogeneity of HRs across groups. (C) Kaplan-Meier survival curves of low and (D) high expression of *FOXA1* among BC patients with varying *U2SURP* expression levels. R version 3.6.1 was used for creation of the figure. BC, breast cancer; HR, hazard ratio; CI, confidence interval.

and BC OS. Meanwhile, *U2SURP* was also found to be significantly associated with BC survival (38).

Our study has several advantages. First, to our knowledge, this is the first study of the relationship between lncRNA-lncRNA interaction and the OS of BC. The *RP11-10E18.7*×*RP11-481C4.2* interaction provides potential evidence that complex disease is driven by intricate association patterns. Second, our study used co-expression analysis to find gene-gene interactions related to lncRNAs and impacting BC OS, which was a comprehensive evaluation of lncRNAs. Third, for the lncRNA-lncRNA interaction analysis, we applied the most conservative Bonferroni correction to control for false positives.

The study has some limitations. First, our study lacked independent validation. Additional available public databases and further researches are warranted. Second, biological evidence requires further functional experiments of lncRNAs, not just our statistical evidence. This association should be interpreted with caution.

## Conclusions

Our study identified *RP11-10E18.7*×*RP11-481C4.2* and *FOXA1*×*U2SURP* interactions as potential biomarkers for BC prognosis. Our findings elucidated potential molecular mechanisms of BC progression under complex association patterns and provided potential dynamic and reversible therapeutic targets for BC patients.

## Acknowledgments

*Funding:* This study was funded by Outstanding Young Medical Talents Program of Pudong Health Bureau of Shanghai (No. PWRq2020-40).

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## Footnote

*Reporting Checklist:* The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1941/rc

*Peer Review File:* Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1941/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1941/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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**Cite this article as:** Zhang W, Wang Y, Deng S, Zhu YC. LncRNA RP11-10E18.7 cooperates with lncRNA RP11-481C4.2 to affect the overall survival of breast cancer patients: a TCGA-based retrospective study. Transl Cancer Res 2023;12(11):3156-3165. doi: 10.21037/tcr-23-1941

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