

Upregulated CCNE1 Correlates with Poor Prognosis, Tumor Immune Infiltration and Escape in Breast Cancer

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Research article

Keywords: CCNE1, prognosis, immune infiltration, immune escape, breast cancer

Posted Date: October 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-966772/v1>

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Abstract

Background

Breast cancer (BC) is the most common malignant tumor in women and widely known for its poor prognosis. More and more research has discovered that cyclin E1 (CCNE1) plays an important role in progression of various types of cancer. But its specific mechanism in BC progression still needs further research to explore.

Methods

At first, we determined the expression and prognostic value of CCNE1 through The Cancer Genome Atlas (TCGA) database and The Genotype-Tissue Expression (GTEx) data. Then, we predicted the upstream non-coding RNAs of CCNE1 through StarBase, GEPIA, and Kaplan-Meier plotter database. We further studied the correlation of CCNE1 expression with BC immune cell infiltration, biomarkers of immune cells and immune checkpoints expression through TIMER and GEPIA databases.

Results

The results suggested that CCNE1 was significantly upregulated in BC and its high expression was correlated with poor prognosis in BC patients. Next, we identified long noncoding RNA (lncRNA) LINC00511 / microRNA-195-5p (miR-195-5p) / CCNE1 axis as the most potential pathway that could regulate CCNE1 expression in BC through StarBase, GEPIA, and Kaplan-Meier plotter database. Furthermore, our in-depth research discovered that CCNE1 expression level was significantly correlated with tumor immune cell infiltration, biomarkers of immune cells, and immune checkpoint expression in BC.

conclusions

In summary, high expression level of CCNE1 was significantly correlated with poor prognosis, tumor immune infiltration and escape in BC.

Introduction

BC, as the most frequent female malignant tumor and the second cause of tumor-related death in women, has received more and more worldwide attention[1]. Despite the great improvement has been received in diagnosis and therapy of BC, and significantly improved survival rate in BC patients, there is still great challenge in BC treatment for its recurrence and metastasis[2, 3]. Therefore, the current treatment of BC is still based on early diagnosis, and surgery assisted with radiotherapy, chemotherapy and targeted-therapy[4]. Therefore, we urgently need to further study the specific molecular mechanisms of BC occurrence and development, and discover more meaningful biomarkers to improve the early diagnosis of BC and the prognosis of breast cancer patients.

Tumor immune cell infiltration has been reported to be closely related to the curative effects of chemotherapy, radiotherapy, immunotherapy in cancer treatment and prognosis of cancer patients, including BC[5–7]. The interaction between tumor cells and their microenvironment has got more and more attention because of its important role in tumor progression. It was widely believed that tumor could escape immune system through three processes, including immune elimination, equilibrium and escape, this ability was widely known as tumor immuno-editing[8]. The interaction between different tumor immune cells facilitates this process[9, 10]. It was reported that cancers could be detected only in immune escape phase in clinic after tumor immuno-editing. And, polymorphonuclear cells, dendritic cells, macrophages, B cells, natural killer cells and T cells were all involved in tumor microenvironment, they played important roles in different cancers in varying degrees. For example, more wide immune infiltration was performed in colorectal cancer than BC[11]. This was widely believed to be because of the mutational burden degree, such as melanoma[12, 13]. So, we urgently need more in-depth research on tumor immunity to better apply immunotherapy to tumor treatment.

CCNE1 was widely studied for its role of binding and activating cyclin dependent kinase 2 (CDK2) to promote the transition of the cell cycle from G1 phase to S phase and start cell DNA synthesis[14]. More and more evidence has suggested that high expression level of CCNE1 was significantly correlated with various types of cancer, including bladder cancer[15], ovarian cancer[16] and so on, also, some opposite research had been found[17, 18]. In BC, some research reported that upregulated CCNE1 was significantly correlated with increasing the risk of recurrence and death basal-like and triple receptor–negative BC, however, no significant relationship was found between CCNE1 overexpression and hormone receptor–positive and luminal BC[19]. Also, many researches had reported the role of CCNE1 played in inhibiting cell apoptosis and promoting cellular malignant phenotype in BC[20, 21]. So, CCNE1 may played an important role in progression of BC. Our research aims to further discover its potential mechanism involved in the development of BC, and analyze the relationship between its expression level and the prognosis of BC, tumor immune infiltration and escape.

Materials And Methods

TCGA database

CCNE1 expression data of the all 33 cancer types, including BLCA, BRCA, CESC, CHOL, COAD, ESCA, HNSC, LIHC, LUAD, LUSC, PAAD, READ, STAD, UCEC, KICH, KIRC, KIRP, THCA, ACC, DLBC, GBM, LAML, LGG, MESO, OV, PCPG, PRAD, SARC, SKCM, TGCT, THYM, UCS and UVM, were collected from TCGA database (<https://genome-cancer.ucsc.edu/>). Then we normalized all the data and analyzed the statistical difference between CCNE1 expression of normal and tumor sample in every cancer type through taking advantage of R limmar package[22]. If p value < 0.05, we think the difference is statistically significant.

Prediction of potential upstream miRNA

To predicting the potential upstream miRNAs that could bind to CCNE1, we took advantage of several prediction programs to finish this work, including TargetScan, PITA, miRmap, miRanda, microT, PicTar and RNA22. We downloaded and normalized all the data, chose the miRNAs that appeared in at least two databases at the same time for the further research. And, these chosen as miRNAs of CCNE1 would be subjected to further correlation analysis.

StarBase database

StarBase database (<http://starbase.sysu.edu.cn/>) is a bioinformatics database professionally used to analyze miRNA-related research[23]. We took advantage of StarBase to predict the upstream lncRNAs of miR-195-5p and analyze the correlation between LINC00511 and miR-195-5p, miR-195-5p and CCNE1, LINC00511 and CCNE1. And, the expression level of miR-195-5p was determined through StarBase database.

Kaplan-Meier plotter database

As a professional bioinformatics web database, Kaplan-Meier plotter (<http://kmplot.com/analysis/>) is widely used to analyze the correlation between genes or miRNAs expression and the survival of various cancer types, including BC. We took advantage of this database to analyze the survival of miR-195-5p in BC. If log rank p value < 0.05 , we considered the difference is statistically significant.

GEPIA database

As a professional online bioinformatics tool, GEPIA database (<http://gepia.cancer-pku.cn/>) is widely used in expression and interactive analysis of normal genes based on TCGA and GTEx data[24]. We took advantage of GEPIA to determine the expression level of CCNE1 and LINC00511 in various cancer types. If p value < 0.05 , we think the difference is statistically significant. Overall survival (OS) and disease-free survival (DFS) analysis for CCNE1 in 14 cancer types were conducted by taking advantage of GEPIA database. GEPIA was also used to analyze the prognostic value of LINC00511 in BC. If log rank p value < 0.05 , we considered the difference is statistically significant. It was identified to be statistically significant, if $|R| > 0.1$ and p value < 0.05 at same time.

TIMER database

TIMER (<https://cistrome.shinyapps.io/timer/>) is a professional online bioinformatics database and widely known for its role in analysis of tumor immune infiltration cells[25]. We took advantage of this tool to conduct the analysis of correlation between the expression level of CCNE1 and the infiltration level of tumor immune cell or the expression level of tumor immune checkpoints in BC. It was identified to be statistically significant, if p value < 0.05 .

Statistical analysis

The statistical analysis involved in our research was all automatically calculated through taking advantage of the corresponding online tool listed above. It was identified to be statistically significant, if p value < 0.05 or log rank p value < 0.05 .

Results

1. Analysis of CCNE1 expression level in pan-cancer types

First, we explore CCNE1 expression in a total of 33 cancer types through TCGA database. The results suggested that CCNE1 was significantly upregulated in 18 cancer types (BLCA, BRCA, CESC, CHOL, COAD, ESCA, HNSC, LIHC, LUAD, LUSC, PAAD, READ, STAD, UCEC, KICH, KIRC, KIRP, THCA) compared to normal samples, and no significant difference was discovered in ACC, DLBC, GBM, LAML, LGG, MESO, OV, PCPG, PRAD, SARC, SKCM, TGCT, THYM, UCS and UVM (Figure 1A). To further verify CCNE1 expression in the 18 cancer types, we took advantage of GEPIA database to finish this work. And, high expression level of CCNE1 was discovered in BLCA, BRCA, CESC, CHOL, COAD, ESCA, HNSC, LIHC, LUAD, LUSC, PAAD, READ, STAD and UCEC compared with normal samples, no significant difference was observed in KICH, KIRC, KIRP and THCA (Figure 1B-1P). In summary, CCNE1 was significantly upregulated in the 14 cancer types, including BLCA, BRCA, CESC, CHOL, COAD, ESCA, HNSC, LIHC, LUAD, LUSC, PAAD, READ, STAD and UCEC. This suggested that CCNE1 may play a very important role in improving the development of the 14 types of cancer.

2. The prognostic roles CCNE1 played in pan-cancer types

Furthermore, we analyzed the prognostic value of CCNE1 in the upon 14 types of cancer (BLCA, BRCA, CESC, CHOL, COAD, ESCA, HNSC, LIHC, LUAD, LUSC, PAAD, READ, STAD, UCEC) through GEPIA database. OS and DFS were included to evaluate its prognostic value. The results suggested that high expression level of CCNE1 in BRCA, LIHC and LUAD had more unfavorable prognosis than downregulation of CCNE1, but no significant difference was discovered in the rest types of cancer (Figure 2). For DFS, we find that upregulation of CCNE1 suggested poor prognosis in BRCA, LIHC and UCEC, also no significant difference was observed in the other types of cancer (Figure 3). Taken together, CCNE1 may be a potential biomarker for predicting the poor prognosis of BC.

3. MiR-195-5p was predicted to be the upstream miRNA of CCNE1 in BC

MiRNAs have been widely studied for its role of inhibiting its target gene expression through binding to the 3'UTR of mRNA. We speculated that CCNE1 can also be regulated by miRNAs, so we predicted the potential upstream miRNAs that can bind to it through StarBase database. And, we found out 26 potential miRNAs that may can bind to CCNE1 (Figure 4A). Next, according to the specific mechanism of action between miRNAs and target gene, their expression levels should be negatively correlated. Based on this principle, we finally selected the following 5 miRNAs, including miR-26a-5p, miR-26b-5p, miR-101-3p, miR-195-5p and miR-497-5p (Figure 4B). No significant expression level correlation was found between the rest of miRNAs and CCNE1. Among the 5 selected miRNAs, we found that miR-195-5p has the most

significant relevance and expression relationship with CCNE1. So, we chose miR-195-5p as the first choice for the following research. Furthermore, we determined miR-195-5p expression and its prognostic value in BC. The results suggested that miR-195-5p was significantly downregulated in BC compared to normal samples (Figure 4C), and, its expression level was significantly negatively correlated with CCNE1 expression level (Figure 4D). Also, high expression level of miR-195-5p was positively correlated with favorable prognosis in BC patients (Figure 4E). Summarize the above results, miR-195-5p might be the most potential miRNA that can regulated CCNE1 expression in BC.

4. LINC00511 was predicted to be the upstream lncRNA of miR-195-5p in BC

For further research, we screened the potential lncRNA upstream of miR-195-5p in BC through the StarBase database. A total of 97 lncRNAs that may bind to miR-195-5p were screened out (Figure 5A). It was widely known that lncRNA may play a role of the competing endogenous RNA (ceRNA) in the progression of various cancers. Based on this mechanism, the expression of lncRNA should be negatively correlated with the miRNA expression level and positively correlated with the mRNA expression level. So, we verified the expression levels of these 97 lncRNAs in BC through GEPIA database. And, the results suggested that only the 4 lncRNAs (HOXC-AS3, LINC00511, LINC00665, TRPM2-AS) were significantly upregulated in BC (Figure 5B-E). Next, we analyzed the correlation between the 4 lncRNAs and miR-195-5p or CCNE1. We find out that only LINC00511 expression was negatively correlated with miR-195-5p expression and positively correlated with CCNE1 expression at the same time (Figure 5F). So, we chose LINC00511 as the upstream lncRNA for the next research. Furthermore, we verified this result and explored the potential prognostic value of LINC00511. And, LINC00511 expression level was significantly negatively correlated with miR-195-5p expression level (Figure 5G) and positively correlated with CCNE1 expression (Figure 5H). Also, high expression level of LINC00511 predicted the poor prognosis in BC patients (Figure 5I). Taken together, LINC00511 might upregulated CCNE1 expression through competitively binding to miR-195-5p and inhibiting its expression in BC.

5. Analysis of the correlation between CCNE1 and immune cell infiltration in BC

CCNE1, as a member of cyclin, was believed to be closely related to protein synthesis and DNA replication. Therefore, we boldly assumed that it is also inseparable from tumor cell immunity. So, we analyzed the correlation between CCNE1 and immune cell infiltration in BC through TIMER database to investigate whether CCNE1 could be a potential biomarker for immunotherapy in BC. We compared the tumor immune cell infiltration level in BC with various somatic copy number alterations (SCNA) of CCNE1. The results suggested that in addition to CD8+ T cell, normal copy number or deletions or amplifications of CCNE1 was observed to be correlated with increased immune cell infiltration in BC, including B cell, CD4+ T cell, macrophage, neutrophil, and dendritic cell (Figure 6A). Next, we determined

the relationship between CCNE1 expression level and immune cell infiltration level in BC. We found out that high expression level of CCNE1 was significantly positively with immune cell infiltration level in BC, including B cell, macrophage, neutrophil, and dendritic cell, and, no significant difference was observed in CD4+ T cell and CD8+ T cell (Figure 6B-G). So, these findings suggested that CCNE1 may play a very significant role in immune cell infiltration in BC.

6. Analysis of the correlation between CCNE1 expression level and biomarkers of immune cell in BC

Furthermore, we analyzed the relationship between CCNE1 and biomarkers of immune cell in BC through GEPIA database, to better verify the correlation of CCNE1 with tumor immunity in BC. As shown in Table 1, CCNE1 was significantly positively correlated with the biomarkers of B cell (CD19), CD8+ T cell (CD8B), M1 macrophage (IRF5), M2 macrophage (CD163 and MS4A4A), Neutrophil (CEACAM8 and CCR7). And, CCNE1 was negatively correlated with the biomarker of Dendritic cell (CD1C), no significant difference was observed between CCNE1 and CD4+ T cell biomarker. In summary, CCNE1 was still significantly positively related to immune cell infiltration in BC.

Table 1
Correlation analysis between CCNE1 and biomarkers of immune cells in BC determined by GEPIA database

Immune cell	Biomarker	R-value	P-value
B cell	CD19	0.13	2.8E-05***
	CD79A	0.095	0.0017
CD8 ⁺ T cell	CD8A	0.096	0.0016
	CD8B	0.15	7.9E-07***
CD4 ⁺ T cell	CD4	0.078	0.011
M1 macrophage	NOS2	0.088	0.0037
	IRF5	0.19	2.9E-10***
	PTGS2	0.099	0.001
M2 macrophage	CD163	0.23	4.8E-15***
	VSIG4	0.028	0.35
	MS4A4A	0.13	1.2E-05***
Neutrophil	CEACAM8	0.11	0.00039***
	ITGAM	0.011	0.72
	CCR7	0.12	9.6E-05***
Dendritic cell	HLA-DPB1	-0.057	0.06
	HLA-DQB1	0.034	0.26
	HLA-DRA	0.045	0.14
	HLA-DPA1	-0.038	0.22
	CD1C	-0.11	0.00017***
	NRP1	-0.1	0.00068
	ITGAX	0.087	0.0041
***p value < 0.001.			

7. Analysis of the correlation of CCNE1 expression level with immune checkpoints in BC

PD1 / PD-L1 and CTLA-4 are widely known for the role of immune checkpoints they played in tumor immune escape. Through upon research, we found that CCNE1 was correlated with tumor immune in BC. So, we determined the relationship between CCNE1 expression and immune checkpoints through TIMER database. The results suggested that the expression level of CCNE1 was significantly positively consistent with PD1, PDL1 and CELA-4 (Figure 7A-C). And, the positive correlation between CCNE1 and PD1 was also observed through GEPIA database (Figure 7D-F). Taken together, we considered that CCNE1 may promote the progression of BC through mediating tumor immune escape. CCNE1 might be the potential target for BC tumor immunotherapy.

Discussion

BC is widely known as one of the most common women malignant tumor all over the world, and its mortality rate ranks second in female cancers due to the annual growth[26, 27]. In the recent years, great achievements have been got in the diagnosis and therapy of BC, its mortality rate has decreased[28]. BC is also widely known as a highly heterogeneous tumor and has various types of etiology and pathological performance in different patients[29]. More and more evidence suggested that the prognosis of BC was significantly correlated with tumor immunity[30]. And, some research reported that lots of inflammatory cells could infiltrate in the tumor microenvironment of BC[31]. A lot of evidence suggested that CD8⁺ T cell was significantly related to immune escape in BC, and, CD8⁺ T cell and CD4⁺ T cell infiltration was greatly correlated with the prognosis of BC patients[32]. Macrophage also played a very important role in tumor immune infiltration and was responsible for cleaning up cell debris and antigen response in BC[33]. Therefore, more in-depth research on tumor immunity will provide more guidance for the treatment and prognosis of BC.

lncRNAs is a group of RNA that molecules with transcripts longer than 200 nt[34]. They are not involved in encoding proteins, but played a role of regulating the expression level of target genes at different stages in progression of tumors, including epigenetic, transcriptional, post-transcriptional regulation and so on[34]. More and more research found that abnormally expressed lncRNAs was significantly correlated with poor prognosis and cell proliferation, invasion, apoptosis of BC[35]. Such as, lncRNA-Hh was reported that could promote the generation of tumor stem cell in twist-positive BC through activating the hedgehog signaling pathway[36]. Upregulated lncRNA-HOXA11-AS was reported to be involved in promoting cell invasion and migration in BC[37]. lncRNAs is receiving more and more attention for the role it played in tumor immunity[38], and, more and more evidence suggested that the types and number infiltrating immune cells were significantly correlated with the prognosis of BC[39, 40].

In this study, we first analyzed the expression level of CCNE1 in pan-cancer types, and we found that CCNE1 was significantly upregulated in in the 14 cancer types, including BLCA, BRCA, CESC, CHOL, COAD, ESCA, HNSC, LIHC, LUAD, LUSC, PAAD, READ, STAD and UCEC. Next, the analysis of prognosis value of CCNE1 in the 14 cancer types was conducted by GEPIA database. The results suggested that upregulation of CCNE1 was correlated with poor prognosis in BRCA, LIHC, LUAD and UCEC. For further research, we conducted the prediction of upstream noncoding RNAs of CCNE1. And, miR-195-5p was

chosen as the upstream miRNA of CCNE1, LINC00511 was predicted as the upstream lncRNA of miR-195-5p. The expression and correlation analysis suggested that miR-195-5p was downregulated in BC and negatively correlated with CCNE1 expression, its downregulation was also related to poor prognosis of BC patients. LINC00511 was found significantly upregulated in BC and negatively correlated with miR-195-5p expression. At the same time, the expression level of LINC00511 was positively correlated with CCNE1 expression and its upregulation was significantly related to poor prognosis of BC patients. This finding was fully in line with the mechanism of ceRNA. So, we think that LINC00511 / miR-195-5p axis is the most potential that could regulate CCNE1 expression in BC. Furthermore, our research in the correlation between CCNE1 and tumor immune infiltration suggested that CCNE1 was significantly positively with immune cell infiltration level in BC, including B cell, macrophage, neutrophil, and dendritic cell. CCNE1 was also positively correlated with some biomarkers of these immune cells, including B cell (CD19), CD8+ T cell (CD8B), M1 macrophage (IRF5), M2 macrophage (CD163 and MS4A4A), Neutrophil (CEACAM8 and CCR7). This indicated that CCNE1 may played a very important role in tumor immune infiltration of BC. At last, we determined the relationship between CCNE1 and tumor immune escape of BC. And, the results suggested that upregulated CCNE1 was significantly correlated with PD1, PD-L1 and CTLA-4 in BC. So, CCNE1 might play an important role in immune escape of BC and it might be a potential target for BC tumor immunotherapy. In summary, CCNE1 was significantly upregulated in BC and correlated with poor prognosis of BC patients. The LINC00511 / miR-195-5p axis was the most potential axis that regulated CCNE1 expression in BC (Figure 8). CCNE1 was also significantly related to tumor immune infiltration and escape in BC, it might become the new potential target for BC tumor immunotherapy. We still need more experiments and clinical data to prove this in future.

Conclusion

CCNE1 was upregulated by LINC00511 / miR-195-5p axis and correlated with poor prognosis, immune cell infiltration and escape in BC.

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of supporting data

All data involved in this study are available from corresponding author based on reasonable request.

Competing interests

No conflict of interests was declared.

Funding

This research was supported by National Nature Science Foundation of China Youth Fund Project (82003290).

Authors' contributions

JF, YH and DL designed this study and completed this manuscript writing. SW, MZ, YW and SQ downloaded and analyzed the data involved in this study from the databases. XL and XPL coordinated all work and carried out quality control. All authors reviewed and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

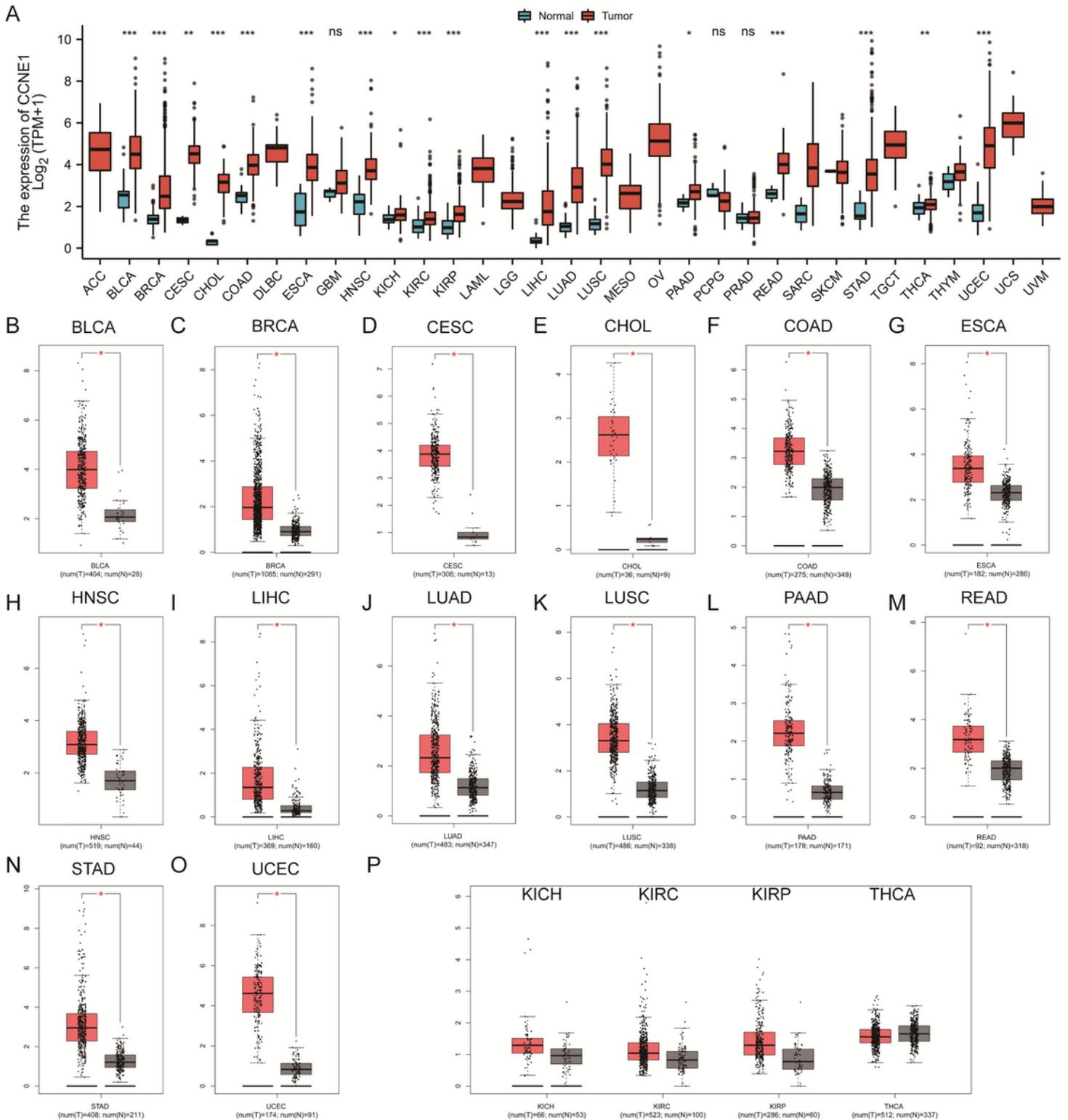


Figure 1

CCNE1 expression analysis in pan-cancer types. A. CCNE1 expression level in 33 cancer types based on TCGA database; B – P. CCNE1 expression in BLCA (B), BRCA (C), CESC (D), CHOL (E), COAD (F), ESCA (G), HNSC (H), LIHC (I), LUAD (J), LUSC (K), PAAD (L), READ (M), STAD (N), UCEC (O), KICH, KIRC, KIRP, THCA (P) based on TCGA and GTEx data. (ACC: Adrenocortical Carcinoma; BLCA: Bladder Urothelial Carcinoma; BRCA: Breast Invasive Carcinoma; CESC: Cervical Squamous Cell Carcinoma and Endocervical

Adenocarcinoma; CHOL: Cholangio Carcinoma; COAD: Colon Adenocarcinoma; DLBC: Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; ESCA: Esophageal Carcinoma; GBM: Glioblastoma Multiforme; HNSC: Head and Neck Squamous Cell Carcinoma; KICH: Kidney Chromophobe; KIRC: Kidney Renal Clear Cell Carcinoma; KIRP: Kidney Renal Papillary Cell Carcinoma; LAML: Acute Myeloid Leukemia; LGG: Brain Lower Grade Glioma; LIHC: Liver hepatocellular Carcinoma; LUAD: Lung Adenocarcinoma; LUSC: Lung Squamous Cell Carcinoma; MESO: Mesothelioma; OV: Ovarian Serous Cystadenocarcinoma; PAAD: Pancreatic Adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate Adenocarcinoma; READ: Rectum Adenocarcinoma; SARC: Sarcoma; SKCM: Skin Cutaneous Melanoma; STAD: Stomach Adenocarcinoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine Corpus Endometrial Carcinoma; UCS: Uterine Carcinosarcoma; UVM: Uveal Melanoma; *p value < 0.05; **p value < 0.01; ***p value < 0.001).

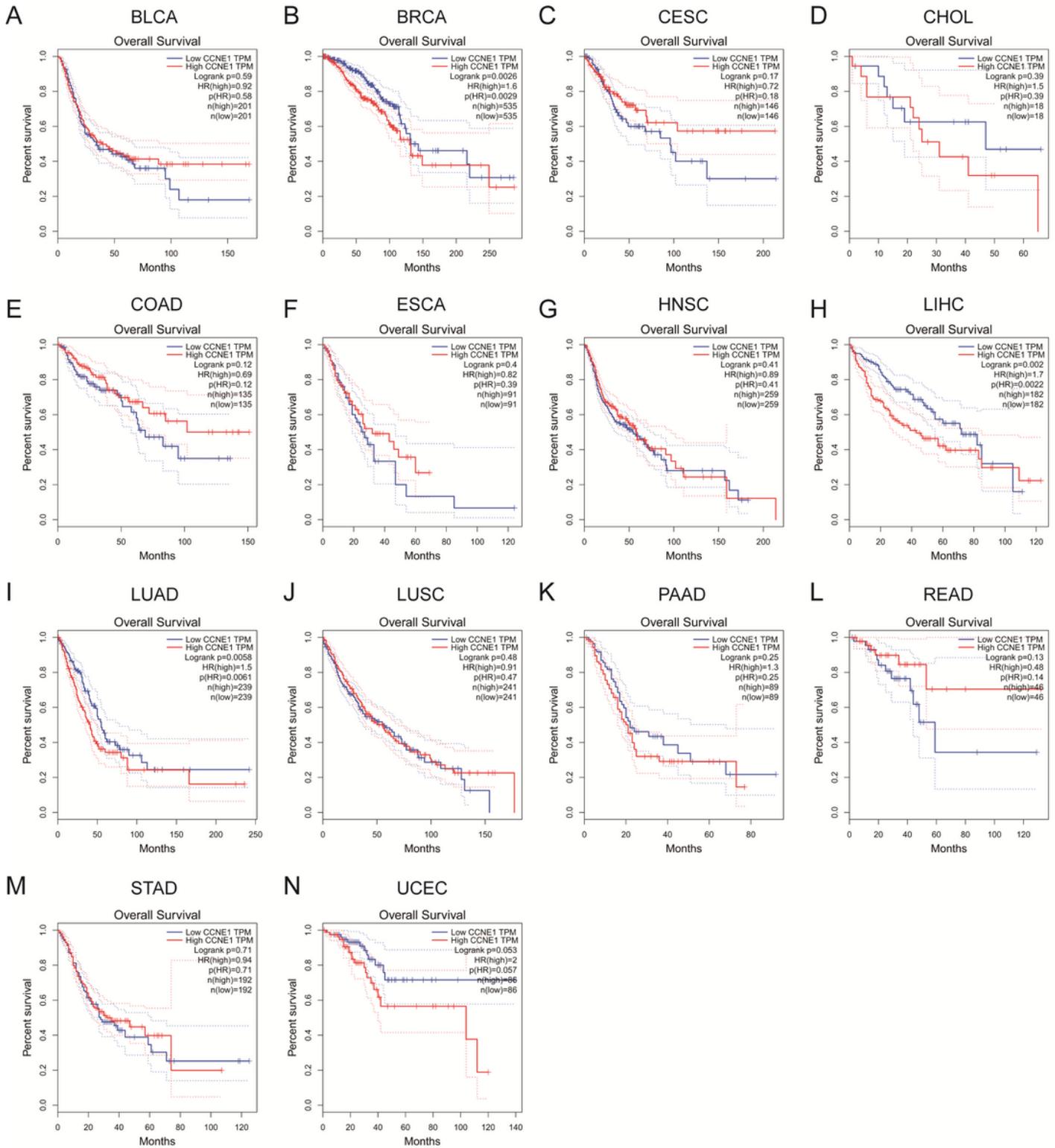


Figure 2

Correlation analysis of CCN1 expression with OS in various cancer types based on GEPIA database. A. BLCA; B. BRCA; C. CESC; D. CHOL; E. COAD; F. ESCA; G. HNSC; H. LIHC; I. LUAD; J. LUSC; K. PAAD; L. READ; M. STAD; N. UCEC.

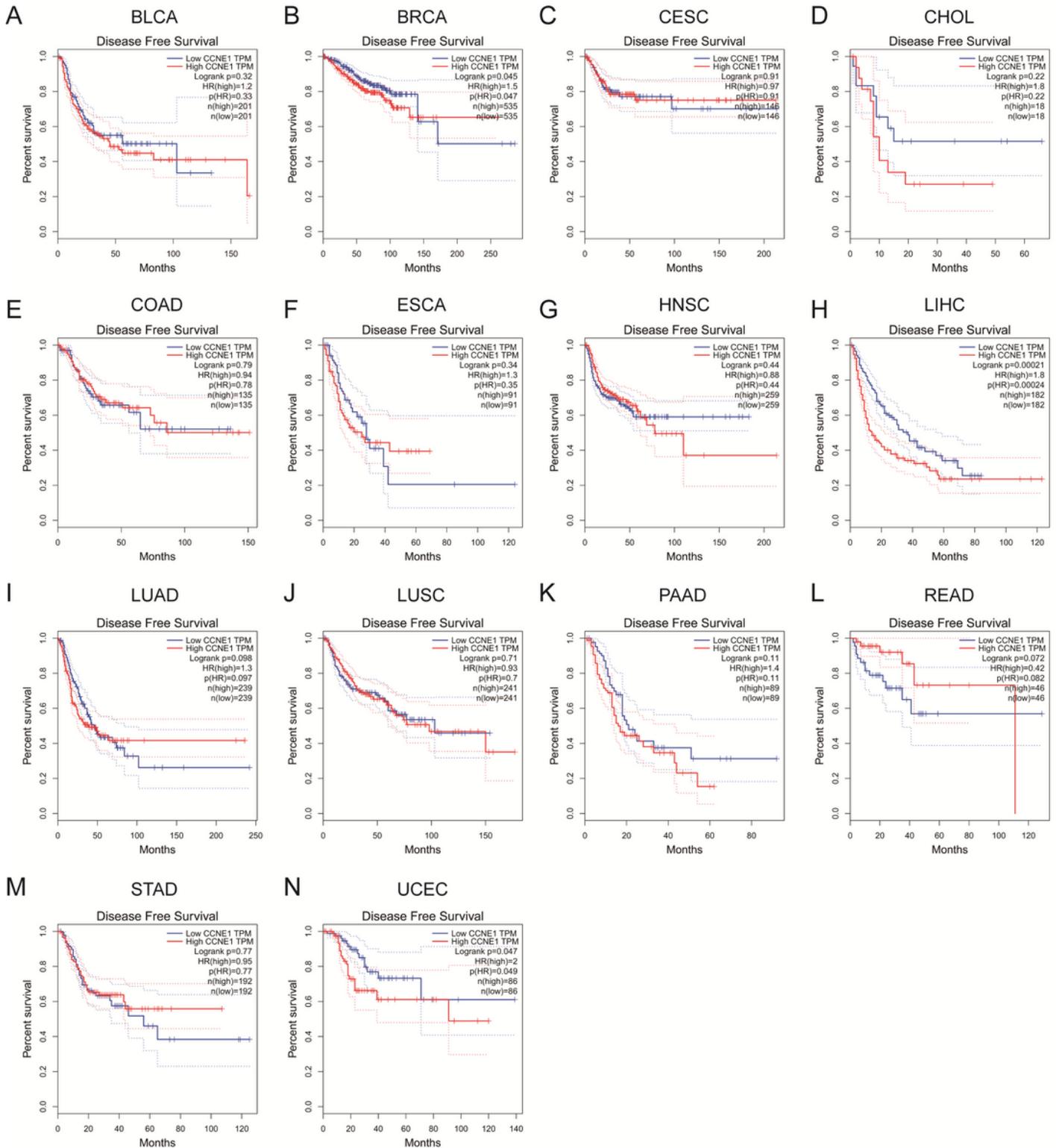


Figure 3

Correlation analysis of CCN1 expression with DFS in various cancer types based on GEPIA database. A. BLCA; B. BRCA; C. CESC; D. CHOL; E. COAD; F. ESCA; G. HNSC; H. LIHC; I. LUAD; J. LUSC; K. PAAD; L. READ; M. STAD; N. UCEC.

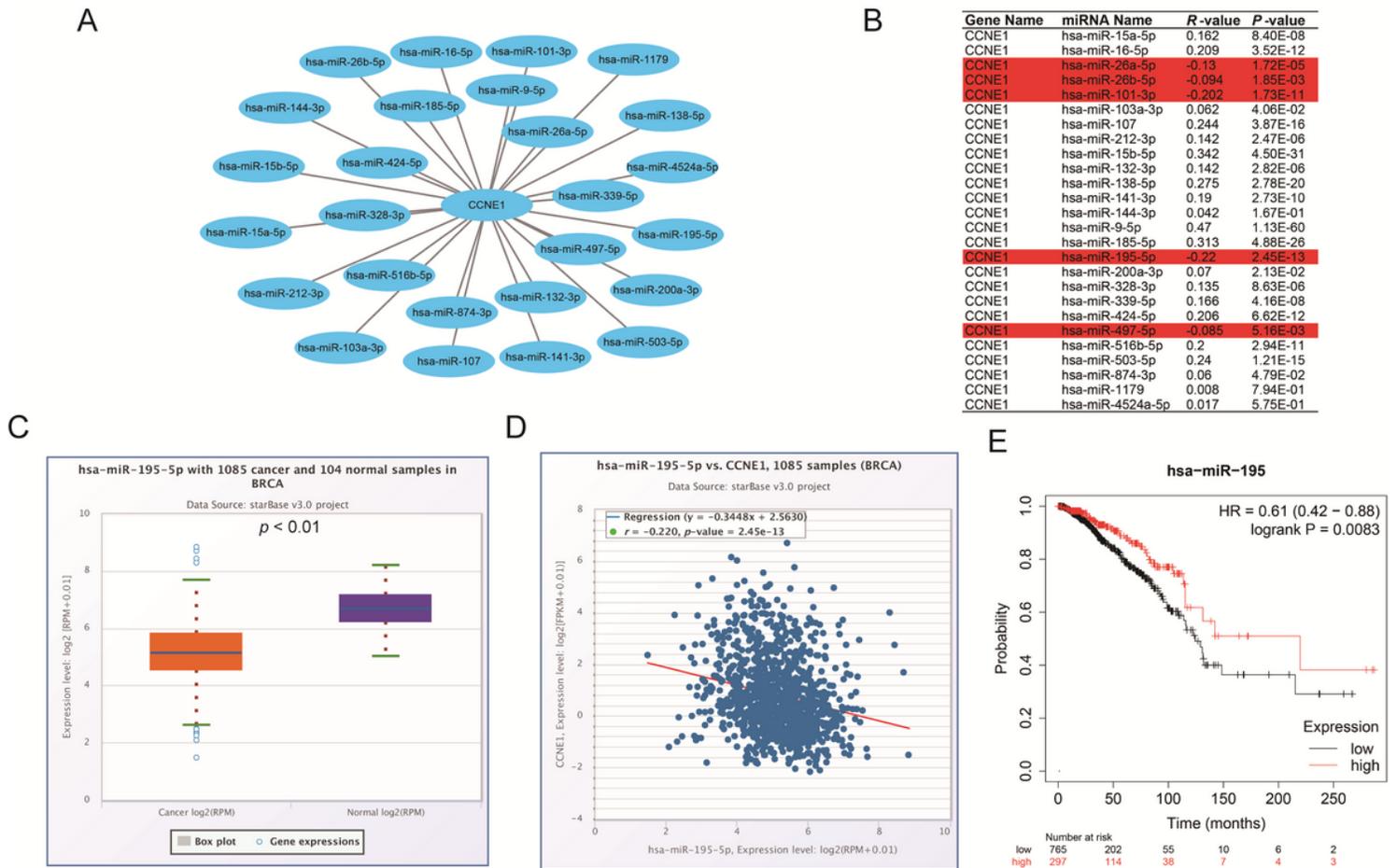


Figure 4

miR-195-5p was predicted to be the potential upstream miRNA of CCNE1. A. miRNA – CCNE1 regulatory network; B. Correlation analysis of CCNE1 and predicted miRNAs expression in BC based on StaiBase database; C. miR-195-5p expression in BC; D. Correlation analysis of miR-195-5p expression with CCNE1 expression in BC based on StaiBase database; E. Prognostic value of miR-195-5p in BC based on Kaplan-Meier plotter.

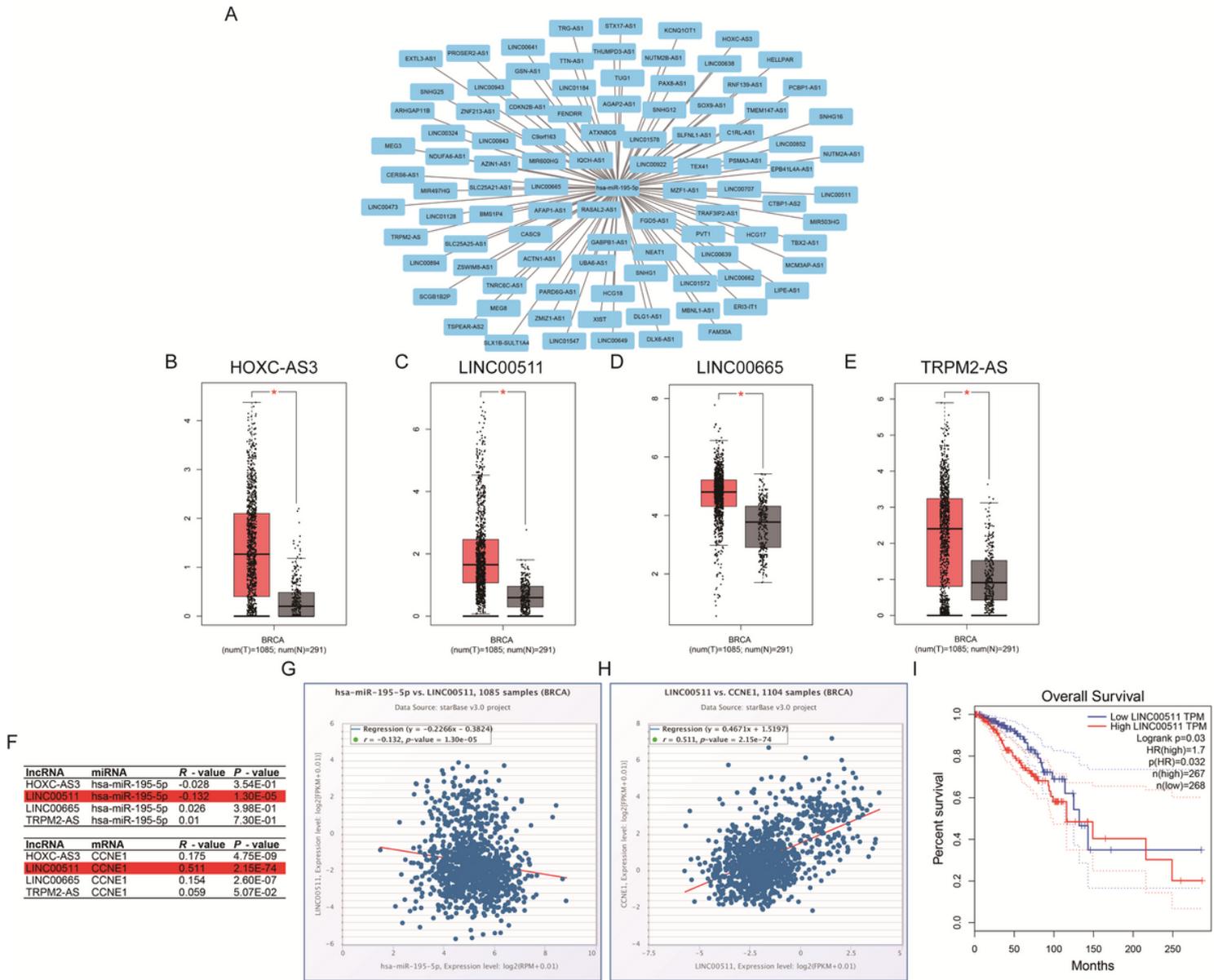


Figure 5

LINC00511 was predicted to be the potential upstream lncRNA of miR-195-5p. A. lncRNA – miR-195-5p regulatory network; B - E. Predicted lncRNAs expression in BC, HOXC-AS3 (B), LINC00511 (C), LINC00665 (D), TRPM2-AS (E); F. Correlation analysis of predicted lncRNAs expression with miR-195-5p or CCNE1 expression in BC; G. Correlation analysis of LINC00511 expression with miR-195-5p expression in BC; H. Correlation analysis of LINC00511 expression with CCNE1 expression in BC; I. Prognostic value of LINC00511 in BC. (*p value < 0.05).

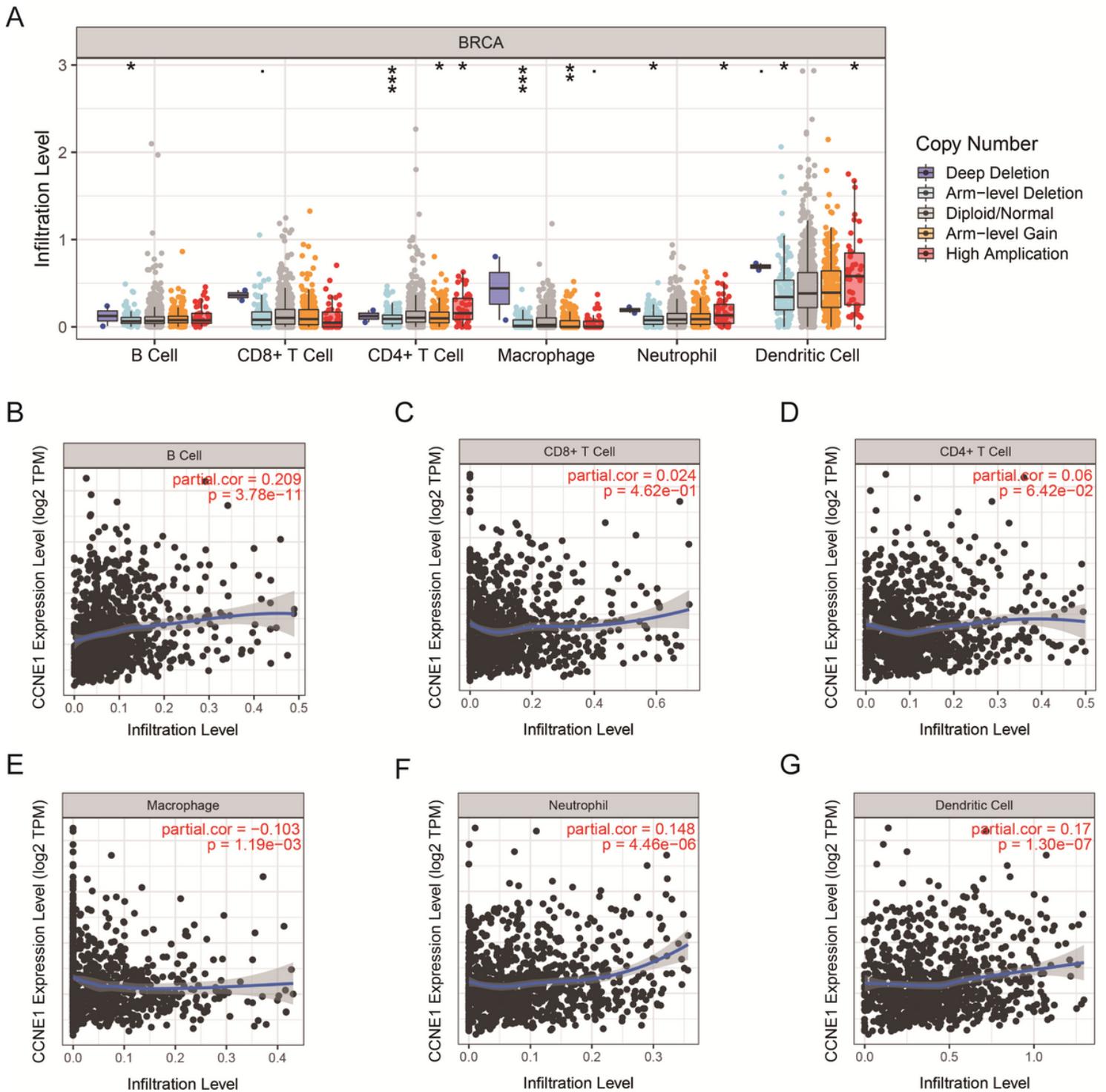


Figure 6

Correlation analysis of CCNE1 with tumor immune cell infiltration in BC. A. Infiltration level of various immune cells under different copy numbers of CCNE1 in BC; B – G. Correlation analysis of CCNE1 expression with B cell (B), CD4+ T cell (C), CD8+ T cell (D), macrophage (E), neutrophil (F), dendritic cell (G). (*p value < 0.05; **p value < 0.01; ***p value < 0.001).

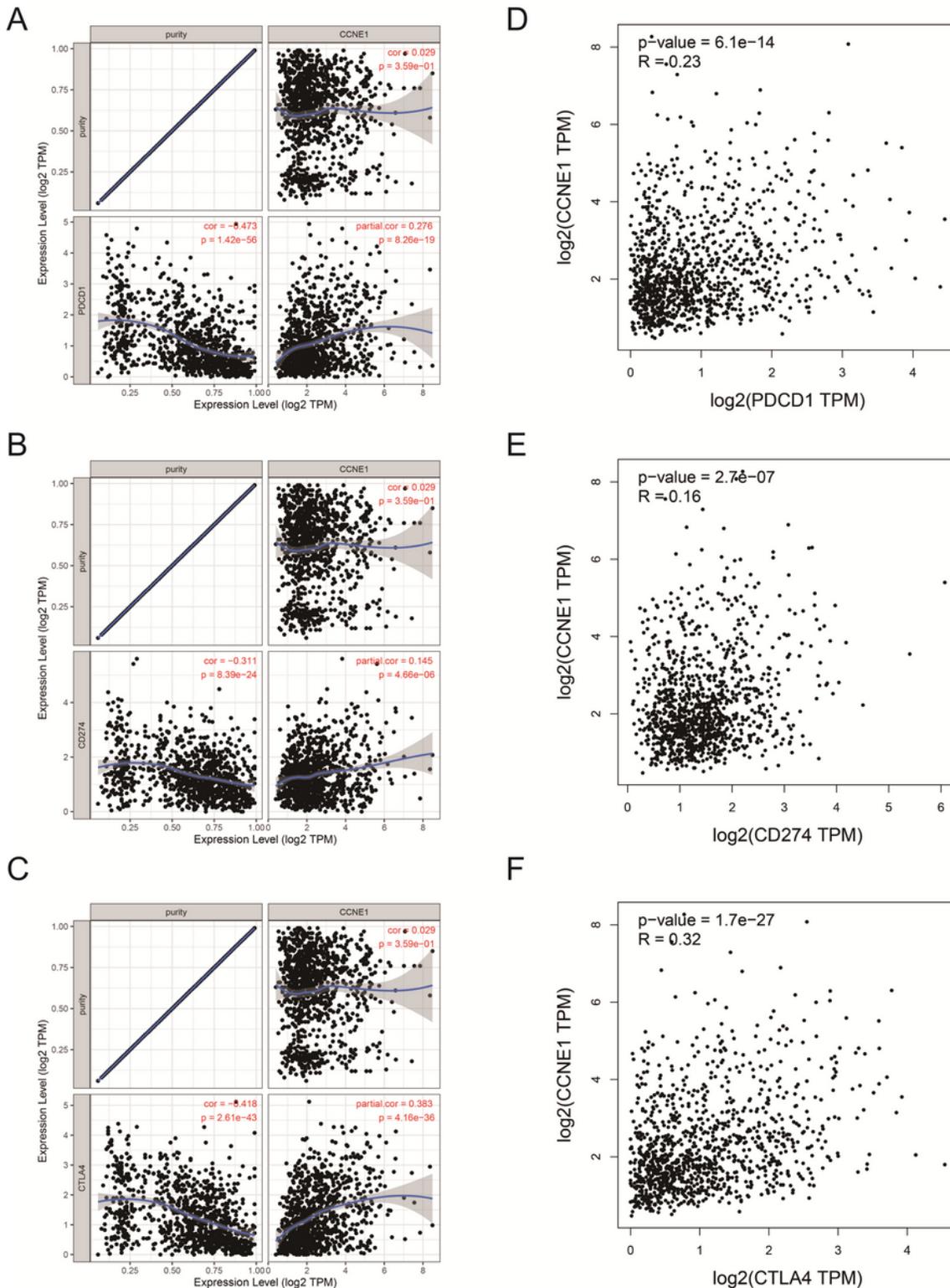


Figure 7

Correlation analysis of CCNE1 expression with immune checkpoints expression in BC. A. Spearman correlation analysis of CCNE1 with PD-1 expression in BC adjusted by purity through TIMER; B. Spearman correlation analysis of CCNE1 with PD-L1 expression in BC adjusted by purity through TIMER; C. Spearman correlation analysis of CCNE1 with CTLA-4 expression in BC adjusted by purity through TIMER; D. Correlation analysis of CCNE1 expression with PD-1 expression in BC based on GEPIA database; E.

Correlation analysis of CCNE1 expression with PD-L1 expression in BC based on GEPIA database; F. Correlation analysis of CCNE1 expression with CTLA-4 expression in BC based on GEPIA database;

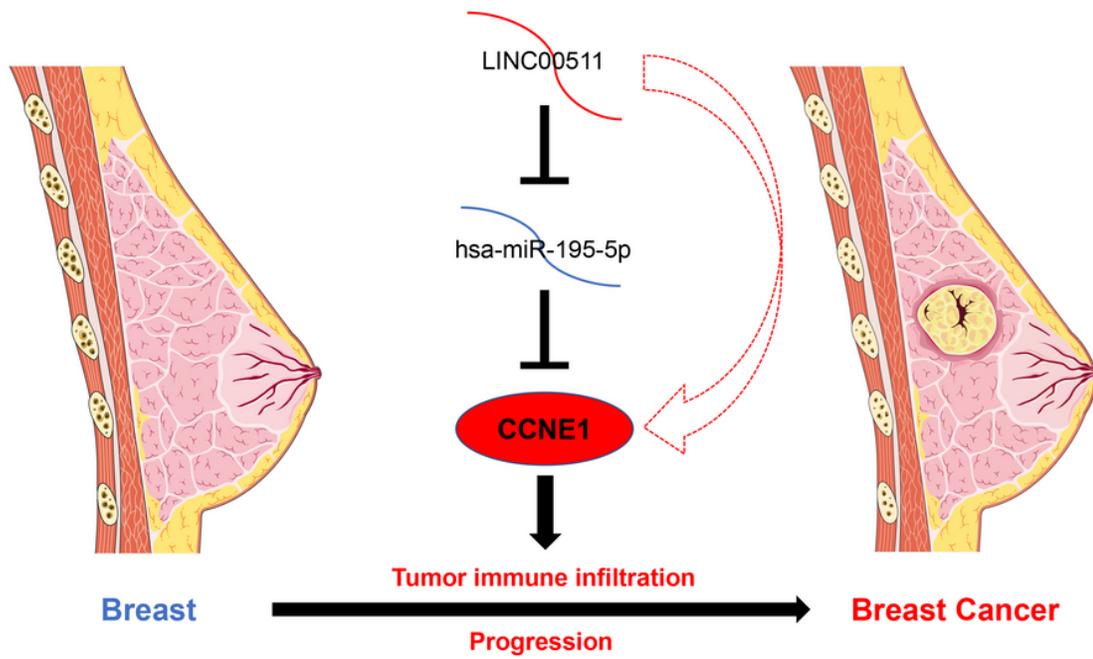


Figure 8

Mechanisms LINC00511 / miR-195-5p / CCNE1 axis played in breast cancer progression.