

Circular RNAs as Biomarkers in Breast Cancer Diagnosis, Prognosis, Molecular Types, Metastasis and Drug Resistance

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Abstract

Breast cancer is one of the leading causes of cancer-related deaths in women worldwide. Circular RNAs (circRNAs), a novel class of endogenous noncoding RNA with a covalently closed continuous loop that lacks the 5'-cap structure and the 3'-poly A tail, are more stable than linear RNAs and less susceptible to degradation by nucleases. CircRNAs are widespread in multiple mammalian genomes and have been detected in various tissues, cells and body fluids. Increasing evidence shows that abnormal expression of circRNAs is involved in the development of a variety of diseases, including breast cancer. Numerous studies have explored the potential of circRNAs as biomarkers in various malignant tumors. In this review, we aim to provide a comprehensive overview of the latest advances in circRNAs as promising biomarkers in the early diagnosis, prognosis, molecular type, metastasis and drug resistance of breast cancer.

Keywords

circRNAs, breast cancer, biomarker, diagnosis, prognosis, molecular type, metastasis, drug resistance

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Introduction

With 2.3 million new cases per year, breast cancer accounts for 11.6% of all cancer cases in 2022, ranking second in global cancer incidence and the fourth leading cause of cancer death worldwide. It is the most common cancer and the leading cause of cancer death among women, posing a serious threat to women's health.¹ At present, neoadjuvant chemotherapy combined with surgery and postoperative systemic therapy have become the accepted strategies for the treatment of breast cancer.² However, breast cancer patients are prone to drug resistance, tumor metastasis and recurrence, and the prognosis of breast cancer patients is not satisfactory.^{3,4} The 5-year survival rate for patients diagnosed with stage I breast cancer is close to 100%, while the 5-year survival rate for patients diagnosed with stage IV breast cancer drops rapidly to 26%.^{5,6} The 5-year survival rate for patients with breast cancer without metastasis is as high as 80%, compared to only about 27% for patients with metastasis. The most common metastatic sites of breast cancer are ipsilateral axillary lymph nodes. The most distant metastatic organs are bone (50%-65%), lung (17%), brain (16%) and liver

(6%), while metastasis to other organs (such as spleen, kidney or uterus) is relatively rare.⁷ Patients with brain metastases have the worst prognosis, with a median survival of only 4-6

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months.⁸ Patients with triple-negative breast cancer (TNBC) have a greatly increased probability of brain metastases, about 30%-50%,⁹ which significantly shortens their survival. Obtaining new clinical tools for early and accurate diagnosis of breast cancer is the key to improve the prognosis for breast cancer patients.

In recent years, with the development of genomics and technologies like liquid biopsy, the understanding of non-coding RNAs (ncRNAs) has been continuously enhanced. ncRNAs are functional transcripts that have limited or no protein-coding potential, mainly including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). They have emerged as promising biomarkers for various diseases, particularly cancer.^{10,11} These RNA molecules are stable in body fluids such as blood, making them suitable for non-invasive liquid biopsy.¹² MiRNAs are 21-23 nucleotides long, single stranded, generated endogenously noncoding RNA molecules that regulate gene expression by binding to target mRNAs.¹³ Some miRNAs are dysregulated in breast cancer and have the potential to serve as biomarkers. Recent studies have confirmed that serum miRNA-1 may serve as a promising noninvasive biomarker for predicting the treatment response in breast cancer patients receiving neoadjuvant chemotherapy.¹⁴ lncRNAs are single-stranded and longer than 200 nucleotides. They can regulate messenger RNAs (mRNAs) stability, translational efficiency, and interfere with post-translational modifications of proteins, playing critical roles in gene regulation and exhibiting differential expression in many cancers.¹⁵ Nowadays, lncRNAs are emerging as crucial biomarkers in the diagnosis and prognosis of various cancers, including breast cancer.¹⁶ For example, LINC00960 is related to triple-negative breast cancer (TNBC) viability, colony formation, organotypic growth, cell migration, and the induction of cell death, affirming LINC00960 as an unfavorable prognostic biomarker promoting TNBC pathogenesis.¹⁷

Unlike linear RNAs (miRNAs, lncRNAs, etc), circRNAs have neither a 5' cap structure nor a 3' tail structure, but are formed of covalent closed rings.^{18,19} CircRNAs with covalent ring structure are not easily degraded by exonuclease and have higher structural stability than linear RNA. CircRNAs are widely distributed across tissues, peripheral blood, exosomes, and other body fluids (such as gastric juice, saliva, and urine).²⁰ Furthermore, with 10 times more diversity in circRNAs variants compared with linear RNA variants, and combined with their high stability, circRNAs are equipped to influence every stage of oncogenesis.²¹ Numerous circRNAs are dysregulated in breast cancer and manifest multiple crucial functions by altering metabolism, immune regulation, angiogenesis, epithelial-mesenchymal transition (EMT), cell cycle regulation, apoptosis etc, and thus involving in breast carcinogenesis, progression and drug resistance of breast cancer, thus highlighting their tremendous potential as biomarkers (Figure 1A).^{22,23} For example, circCARM1, derived from breast cancer stem cells (BCSC), played an important role in breast cancer cell glycolysis by sponging miR-1252-5p which regulates PFKFB2 expression, thus influencing cell migration.²⁴ CircGSK3 β is highly expressed in breast cancer

cell lines and promotes breast cancer cell proliferation, migration, invasion, and immune evasion, by interaction with miR-338-3p and subsequent regulation of PRMT5 and PD-L1.²⁵ Homo sapiens (has)_circ_0000515 was overexpressed in breast cancer tissues. It bound to miR-296-5p, which, in turn, specifically targeted CXCL10. Hsa_circ_0000515/miR-296-5p/CXCL10 axis regulated tumor cell proliferation, angiogenesis, and inflammation in vivo. Inhibition of hsa_circ_0000515 suppressed breast cancer progression by interrupting hsa_circ_0000515-mediated degradation of miR-296-5p.²⁶ It not only serves as a potential biomarker for breast cancer but also provides a target for the future treatment of breast cancer. CircEZH2 could promote EMT of breast cancer in a CXCR4-dependent manner via upregulated KLF5, which was shown to be upregulated in liver metastases in breast cancer and predicted worse prognosis in breast cancer patients.²⁷ The functional mechanisms of circRNAs mainly involve serving as miRNA sponges, protein binding, transcriptional regulation as well as encoding proteins and peptides (Figure 1B), which play significant roles in regulating different molecular pathways.²⁸ A systematic understanding of the functions of circRNAs and their underlying functional mechanisms is conducive to the discovery of specific biomarkers and the exploration of new treatment approaches, thus inspiring cancer management.

In recent years, researchers have conducted extensive studies on the function and functional mechanism of circRNAs in various malignant tumors, providing a variety of potential biomarkers and therapeutic targets for researchers and clinicians. Coupled with their stability and high specificity, circRNAs have unique advantages over traditional tumor markers, including differentiating between benign and malignant diseases, predicting tumor risk and progression, monitoring treatment sensitivity, and early detection of cancer.

To identify relevant studies, we searched the literature on NCBI PubMed with the keywords "(CircRNAs) AND (Breast cancer)" as the screening criterion. Articles with clinical samples published between 2020 and 2024 that exclude basic research were selected and carefully read.

Here, we briefly review the functions of circRNAs in breast cancer and the underlying functional mechanisms, to provide clinicians and researchers with a comprehensive overview of the latest advances in circRNAs acting as biomarkers for breast cancer research regarding diagnosis, prognosis, molecular type, metastasis and drug resistance. We hope to inspire further research on circRNAs to identify ideal biomarkers and therapeutic targets.

CircRNAs as Markers for Early Diagnosis of Breast Cancer

More and more studies have found that circRNAs are abnormally expressed in the blood and tissues of breast cancer patients, suggesting that this abnormal expression of circRNAs may be useful as a diagnostic detection indicator for early breast cancer (Table 1). Homo sapiens (hsa)_circ_0005046 and hsa_circ_0001791 are highly expressed in breast cancer tissues with AUC of 0.77

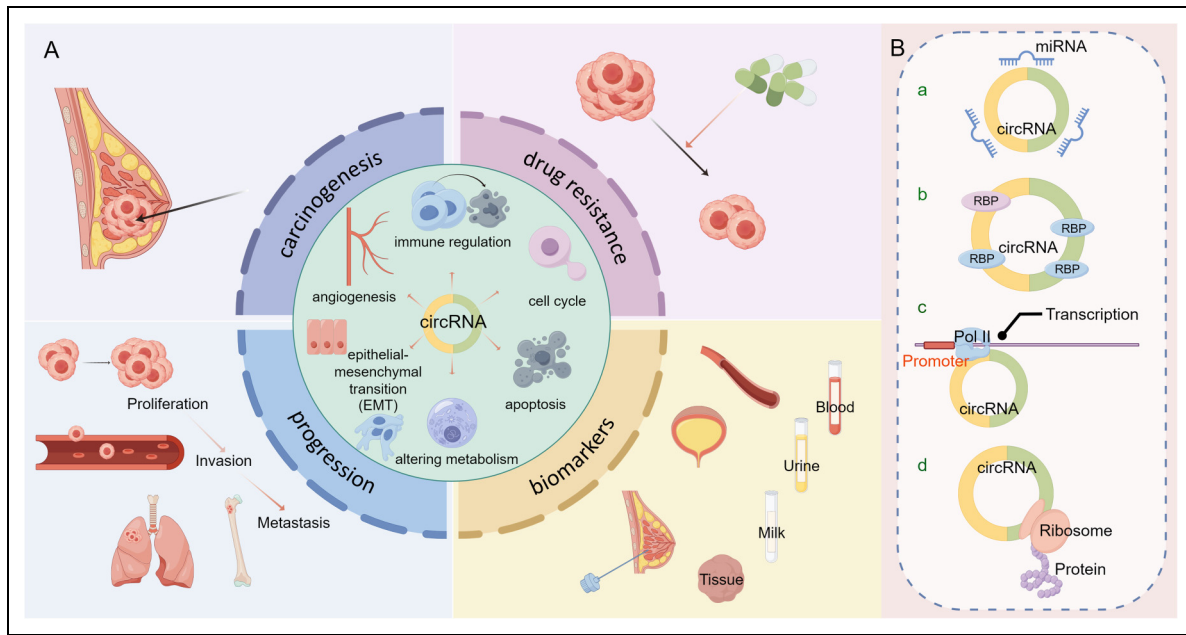


Figure 1. The functions and functional mechanism of circRNAs in breast cancer. (A) CircRNAs manifest multiple functions by altering metabolism, immune regulation, angiogenesis, epithelial-mesenchymal transition (EMT), cell cycle regulation and apoptosis, and thus involve in breast carcinogenesis, progression and drug resistance of breast cancer. Moreover, their potential as biomarkers has been recently highlighted. (B) The functional mechanism of circRNAs. (a) Acting as miRNA sponge, circRNAs are rich in numerous miRNA binding sites and can competitively bind to miRNAs. (b) By binding to proteins, circRNAs affect the functions of RNA-binding proteins (RBPs) and the interactions among RBPs. (c) CircRNAs can upregulate the transcription through interacting with the RNA polymerase II (RNA Pol II) complex. (d) CircRNAs can be translated into proteins. The figure is drawn by Figdraw.

and 1, respectively, which could distinguish breast cancer and adjacent tissues well. The AUC of hsa_circ_0001791 is 1, indicating that hsa_circ_0001791 has a high diagnostic value for breast cancer.²⁹ Circ_0007255 is up-regulated in serum of breast cancer patients with an AUC of 0.7748.³⁰ Studies have shown that in breast cancer tissue, circWHSC1,³¹ circRREB1,³² circ_0009910,³³ circZCCHC2,³⁴ circCAPG,³⁵ circDNAJC11³⁶ and circPFKFB4³⁷ were up-regulated. Hsa_circ_0069094,³⁸ hsa_circ_0079876,³⁸ hsa_circ_0017650³⁸ and hsa_circ_0017536³⁸ were significantly up-regulated in breast cancer plasma, and circPRMT5³⁹ was significantly up-regulated in breast cancer serum.

The diagnostic value of a single circRNA is limited, and the combined application of multiple markers could improve the diagnostic value. Omid-Shafaat R et al. found that circ-ELP3 was highly expressed while circ-FAF1 was decreased in the serum of breast cancer patients, with the AUC of 0.733 and 0.787, respectively. The sensitivity and specificity of circ-ELP3 and circ-FAF1 were 65%, 64% and 77%, 74%, respectively, but the combined application of circ-ELP3 and circ-FAF1 improved the diagnostic efficacy of breast cancer, with AUC up to 0.891, sensitivity and specificity of 96% and 62%.⁴⁰ When circ_0000745, circ_0001531 and circ_0001640 were combined in whole blood for the diagnosis of breast cancer, the AUC was 0.9130.⁴¹ Studies have shown that in breast cancer tissues, the expression of hsa_circ_103110, hsa_circ_104689 and hsa_circ_104821 is down-regulated, however, the expression of

hsa_circ_006054, hsa_circ_100219 and hsa_circ_406697 were up-regulated. The effect of the combined model was better than that of the single indicator.⁴²

At present, numerous studies have compared circRNAs expression before and after surgery, and found that the expression level of circRNAs decreased or increased significantly after breast tumor resection. For example, the expression levels of circ-ELP3 in postoperative plasma were significantly reduced compared with those in preoperative plasma.⁴⁰ The expression levels of circ-FAF1 in plasma after operation were significantly higher than those before operation.⁴⁰

CircRNAs as Markers to Evaluate the Prognosis of Breast Cancer

The expression level of circRNAs in breast cancer is closely related to the pathological characteristics and survival of breast cancer patients, and could be used as a potential marker to predict the prognosis of breast cancer (Table 2). Studies have shown that the overall survival (OS) of breast cancer patients with high expression of circHMCU,⁴³ exosomal circSIPA1L3,⁴⁴ circRREB1,³² circATP2C1/has_circ_0005797,⁴⁵ has_circ_0000069,⁴⁶ circDNAJC11,³⁶ circ_0008717,⁴⁷ circPFKFB4,³⁷ circPTK2,⁴⁸ circ-EIF6/hsa_circ_0060055,⁴⁹ circRBMS3⁵⁰ and circANKS1B⁵¹ was short, while breast cancer patients with low expression of circRNA-CREIT⁵² was short. TNBC patients with high expression of hsa_circ_102229,⁵³ circWHSC1,³¹

Table 1. CircRNAs in Breast Cancer Diagnosis.

CircRNA	Specimen type	Altered Expression	AUC	Reference
hsa_circ_0005046	BCT	Up-regulated	0.77	29
hsa_circ_0001791	BCT	Up-regulated	1	29
circVHSCI	BCT	Up-regulated	0.968	31
circRREB1	BCT	Up-regulated	0.707	32
circ_0009910	BCT	Up-regulated	0.7544	33
circZCCHC2	BCT	Up-regulated	0.787	34
circCAPG	BCT	Up-regulated	0.8723	35
circDNAJC11	BCT	Up-regulated	0.658	36
circPFKFB4	BCT	Up-regulated	0.667	37
hsa_circ_103110	BCT	Down-regulated	0.63	42
hsa_circ_104689	BCT	Down-regulated	0.61	42
hsa_circ_104821	BCT	Down-regulated	0.6	42
hsa_circ_006054	BCT	Up-regulated	0.71	42
hsa_circ_100219	BCT	Up-regulated	0.78	42
hsa_circ_406697	BCT	Up-regulated	0.64	42
hsa_circ_006054 + hsa_circ_100219 + hsa_circ_406697	BCT	NA	0.82	42
hsa_circ_0069094	BCP	Up-regulated	0.6808	38
hsa_circ_0079876	BCP	Up-regulated	0.6228	38
hsa_circ_0017650	BCP	Up-regulated	0.7586	38
hsa_circ_0017536	BCP	Up-regulated	0.6152	38
circ_0007255	BCS	Up-regulated	0.7748	30
circPRMT5	BCS	Up-regulated	0.9323	39
circ-FAF1	BCS	Down-regulated	0.787	40
circ-ELP3	BCS	Up-regulated	0.733	40
circ-FAF1 + circ-ELP3	BCS	NA	0.891	40
circ_0000745	BCPB	Up-regulated	0.7998	41
circ_0001531	BCPB	Up-regulated	0.8258	41
circ_0001640	BCPB	Up-regulated	0.7161	41
circ_0000745 + circ_0001531 + circ_0001640	BCPB	Up-regulated	0.913	41

BCT: breast cancer tissues, BCP: breast cancer plasma, BCS: breast cancer serum, BCPB: breast cancer peripheral blood, NA: not applicable.

circCAPG,³⁵ circ_0001006,⁵⁴ circTBC1D14⁵⁵ and circWAC⁵⁶ had significantly shorter OS than TNBC patients with low expression. The expression of circWSB1 is up-regulated in breast cancer tissues, and the higher the expression level of circWSB1, the shorter the survival time of patients and the higher the recurrence rate.⁵⁷ Breast cancer patients with high expression of circ_0044234⁵⁸ and TNBC patients with high expression of hsa_circ_001783⁵⁹ had short disease-free survival (DFS). Breast cancer patients with high expression of circCDYL,⁶⁰ circ_0004674,⁶¹ hsa_circ_0067842⁶² and low expression of circ-LARP4⁶³ had short OS and DFS. Clinical data from patients with human epidermal growth factor receptor 2 (HER2) -positive early breast cancer treated with trastuzumab show that patients with high expression of circCDYL2 have shorter OS and DFS.⁶⁴ The expression level of has_circ_0006528 in the tissues of stage III breast cancer patients is higher than that of early-stage breast cancer patients. The relapse-free survival (RFS) and OS of patients with high expression level of has_circ_0006528 were significantly lower than patients with low has_circ_0006528 expression.⁶⁵ The expression of circPAPD4 is down-regulated in breast cancer tissues, and breast cancer patients with low circPAPD4 expression have an unfavorable RFS compared with patients with high circPAPD4 expression.⁶⁶ Breast cancer patients with high circ_0001667⁶⁷ expression and TNBC patients with low circDUSP1⁶⁸

expression showed poor survival rates. Breast cancer patients with high circPRMT5 expression showed short OS and progression-free survival (PFS).³⁹

CircRNAs can Distinguish Between TNBC and non-TNBC

The subtype of triple-negative breast cancer (TNBC) is characterized by the absence of three specific receptors: human epidermal growth factor receptor 2 (HER2), progesterone receptors (PR) and estrogen receptors (ER),⁶⁹ which account for about 15%-20% of all breast cancers.⁷⁰ This subtype is associated with poor prognosis, limited treatment options and higher recurrence rates,⁷¹ with more than 50% of patients relapsing within 3-5 years of diagnosis⁷² and the median OS currently treated being 10.2 months.⁷³ CircRNAs have different expression levels in different molecular types of breast cancer, and could be used as markers to distinguish different molecular types, especially in distinguishing TNBC from non-TNBC (Table 3). Compared with non-TNBC tissues, hsa_circ_0006220,⁷⁴ circ_0044234,⁵⁸ circ_FOXO3,⁷⁵ circNR3C2⁷⁶ and circ_0000977⁷⁷ were significantly down-regulated in TNBC tissues. Compared with luminalA/B and HER2-positive molecular types,

Table 2. CircRNAs in Breast Cancer Prognosis.

CircRNA	Specimen type	Altered Expression	Prognosis	Reference
circHMCU	BCT	Up-regulated	poor OS	43
circANKS1B	BCT	Up-regulated	poor OS	51
exosomal circSIPA1L3	BCT	Up-regulated	poor OS	44
circRREB1	BCT	Up-regulated	poor OS	32
circATP2C1/has_circ_0005797	BCT	Up-regulated	poor OS	45
has_circ_0000069	BCT	Up-regulated	poor OS	46
circDNAJC11	BCT	Up-regulated	poor OS	36
circ_0008717	BCT	Up-regulated	poor OS	47
circRNA-CREIT	BCT	Down-regulated	poor OS	52
circPFKFB4	BCT	Up-regulated	poor OS	37
circPTK2	BCT	Up-regulated	poor OS	48
circ-EIF6/hsa_circ_0060055	BCT	Up-regulated	poor OS	49
circRBMS3	BCT	Up-regulated	poor OS	50
circWSB1	BCT	Up-regulated	poor OS and high recurrence	57
circ_0044234	BCT	Down-regulated	poor DFS	58
circ-LARP4	BCT	Down-regulated	poor OS, poor DFS	63
circCDYL	BCT	Up-regulated	poor OS, poor DFS	60
circ_0004674	BCT	Up-regulated	poor OS, poor DFS	61
hsa_circ_0067842	BCT	Up-regulated	poor OS, poor DFS	62
has_circ_0006528	BCT	Up-regulated	poor RFS and poor OS	65
circPRMT5	BCT	Up-regulated	poor OS, poor PFS	39
circPAPD4	BCT	Down-regulated	poor RFS	66
circ_0001667	BCT	Up-regulated	low survival rate	67
circCDYL2	HER2 + BCT	Up-regulated	poor OS, poor DFS	64
hsa_circ_102229	TNBCT	Up-regulated	poor OS	53
circWHSC1	TNBCT	Up-regulated	poor OS	31
circCAPG	TNBCT	Up-regulated	poor OS	35
circ_0001006	TNBCT	Up-regulated	poor OS	54
circTBC1D14	TNBCT	Up-regulated	poor OS	55
circWAC	TNBCT	Up-regulated	poor OS	56
hsa_circ_001783	TNBCT	Up-regulated	poor DFS	59
circDUSP1	TNBCT	Down-regulated	low survival rate	68

TNBCT: triple-negative breast cancer tissues, BCT: breast cancer tissues, HER2 + BCT: HER2 + breast cancer tissues, OS: overall survival, DFS: disease-free survival, RFS: relapse-free survival, PFS: progression-free survival.

Table 3. CircRNAs in Distinguishing Molecular Types.

CircRNA	Specimen type	Altered Expression	Reference
has_circ_0006220	TNBCT	Down-regulated	74
circ_0044234	TNBCT	Down-regulated	58
circCD44	TNBCT	Up-regulated	78
circBRAF	TNBCT	Up-regulated	79
circZCCHC2	TNBCT	Up-regulated	34
circ-FOXO3	TNBCT	Down-regulated	75
circ_0000977	TNBCT	Down-regulated	77
circNR3C2	TNBCT	Down-regulated	76
circANKS1B	TNBCT	Up-regulated	51
has_circ_001783	TNBCT	Up-regulated	59
circRPPH1/ has-circ-000166	TNBCT	Up-regulated	80

TNBCT: triple-negative breast cancer tissues.

the expression level of circ_0044234 in TNBC is the lowest, and the difference is the greatest between the TNBC with the luminal A type breast cancer.⁵⁸ There was no significant difference in the expression of circCD44 in non-TNBC and corresponding adjacent tissues,

while in TNBC and corresponding adjacent tissues, circCD44 was up-regulated in TNBC tissues, indicating that circCD44 may be a diagnostic marker of TNBC.⁷⁸ CircBRAF,⁷⁹ circZCCHC2,³⁴ circANKS1B,⁵¹ has_circ_001783⁵⁹ and circRPPH1/has_circ_000166⁸⁰ were significantly up-regulated in tumor tissues of TNBC patients.

CircRNAs as Markers to Predict Breast Cancer Metastasis

Lymph node metastasis is the most common mode of breast cancer metastasis, and some circRNAs can be used as markers to predict lymph node metastasis (Table 4). Circ_0000160,⁸¹ circ-FOXO3⁷⁵ and circDUSP1⁶⁸ were significantly down-regulated in breast cancer tissues with lymph node metastasis, and hsa_circ_0000091 was significantly down-regulated in plasma of patients with lymph node metastasis. When plasma hsa_circ_0000091 combined with ultrasound was used to diagnose lymph node metastasis of breast cancer, the diagnostic accuracy was increased.⁸² CircWHSC1⁸³ and circZCCHC2³⁴ are highly expressed in breast cancer tissues with lymph node

Table 4. CircRNAs in Breast Cancer Metastasis.

CircRNA	Metastatic site	Specimen type	Altered Expression	Reference
circ_0000160	ALNM	BCT with ALNM	Down-regulated	81
circWHSCI	ALNM	BCT with ALNM	Up-regulated	83
circDUSP1	ALNM	BCT with ALNM	Down-regulated	68
circZCCHC2	ALNM	BCT with ALNM	Up-regulated	34
circ-FOXO3	ALNM	TNBCT with ALNM	Down-regulated	75
hsa_circ_0000091	ALNM	BCP with ALNM	Down-regulated	82
circEGFR	ALNM	BCALNM tissues	Up-regulated	84
circIKBKB	Bone M	BCT with BOM	Up-regulated	41
circRBMS3	Bone M	BCBOM tissues	Up-regulated	50
circBCBM1	Brain M	BCBRM tissues	Up-regulated	85
circMMP2(6,7)	Brain M	BCBRM tissues	Up-regulated	86
hsa_circ_0007255/circKIF4A	Brain M	BCBRM tissues	Up-regulated	87
circBCBM1	Brain M	BCP with Brain M	Up-regulated	85
circEZH2	LM	BCLM tissues	Up-regulated	27
has_circ_0072305/circLIFR-007	LM	BCLM tissues	Down-regulated	90
hsa_circ_0060467/circMYBL2	LM	BCLM tissues	Up-regulated	89
circROBO1	LM	BCLM tissues	Up-regulated	88

ALNM: axillary lymph node metastasis, Bone M: bone metastasis, BOM: bone metastasis, Brain M: brain metastasis, BRM: brain metastasis, LM: liver metastasis, BCT: breast cancer tissues, BCP: breast cancer plasma, BC: breast cancer.

Table 5. CircRNAs in Breast Cancer Drug Resistance.

CircRNA	Specimen type	Altered Expression	Reference
circ_0006528	ADR-resistive BCT	Up-regulated	91
circ_0001667	ADR-resistive BCT	Up-regulated	92
circ_0044556	ADR-resistive BCT	Up-regulated	93
circATXN7	ADR-resistive BCT	Up-regulated	94
circ-RNF111	PTX-resistive BCT	Up-regulated	97
circ-ABCB10	PTX-resistive BCT	Up-regulated	99
circ_0069094	PTX-resistive BCT	Up-regulated	98
circABCB1	PTX-resistive BCT	Up-regulated	100
circTRIM28	TAM-resistive BCT	Up-regulated	101
circ_UBE2D2	TAM-resistive BCT and exosome	Up-regulated	102
circ-β-TrCP	Trastuzumab-resistive BCS	Up-regulated	103
circ-BGN	Trastuzumab-resistive BCT	Up-regulated	104
circCDYL2	Trastuzumab-resistive HER2 + BCT	Up-regulated	64

BCT: breast cancer tissues, BCS: breast cancer serum, ADR: doxorubicin, PTX: paclitaxel, TAM: tamoxifen.

metastasis, and the expression of circEGFR in breast cancer lymph node metastasis tissues is higher than that in non-metastatic tissues.⁸⁴

Differential expression of circRNAs is also present in breast cancer patients with and without distant metastases. CircIKBKB is not detected in normal breast tissues, and its expression level is upregulated in breast cancer tissues. Moreover, it is higher in metastatic compared to non-metastatic cases. Identifying the expression of circIKBKB in patients with breast cancer is helpful for diagnosis and treatment of patients with breast cancer complicated with bone metastases.⁴¹

CircRBMS3 is highly expressed in breast cancer bone metastases and may be a potential marker for predicting bone metastasis in patients.⁵⁰

CircBCBM1 is significantly upregulated in both breast cancer brain metastases tissue and plasma.⁸⁵ CircMMP2(6,7) is stepwise upregulated from breast cancer tissue without brain metastases, breast cancer tissue with brain metastases to brain metastases tissue of breast cancer.⁸⁶ The level of hsa_circ_0007255/circKIF4A is elevated in brain metastases, and it holds promise as a new biomarker for the diagnosis and treatment of TNBC brain metastases.⁸⁷

CircEZH2,²⁷ circROBO1⁸⁸ and hsa_circ_0060467/circMYBL2⁸⁹ were significantly up-regulated in breast cancer liver metastasis tissues. Has_circ_0072305/CircLIFR-007 was significantly down-regulated in liver metastasis tissues.⁹⁰

CircRNAs as Markers to Assess Sensitivity to Drug Therapy

Drug therapy for breast cancer is effective, but long-term drug therapy may lead to drug resistance, which is unfavorable to the prognosis of breast cancer patients (Table 5). Doxorubicin (ADR) is a broad-spectrum antitumor drug that inhibits DNA and RNA synthesis. Circ_0006528,⁹¹ circ_0001667,⁹² circ_0044556⁹³ and circATXN7⁹⁴ are all up-regulated in ADR-resistant breast cancer tissues and cell lines.

Paclitaxel (PTX) is a common chemotherapy drug for breast cancer. However, with the passage of treatment time, the efficacy and effect of PTX will decline, and breast cancer patients who receive PTX treatment for 6-10 months will develop resistance to PTX.^{95,96} Circ-RNF111,⁹⁷ circ_0069094⁹⁸ and circ-ABCB10⁹⁹ are up-regulated in PTX-resistant breast cancer tissues. CircABCB1 is highly expressed in breast cancer

compared to normal tissues, and is even more expressed in docetaxel-resistant patients than in docetaxel-sensitive patients.¹⁰⁰

Tamoxifen (TAM) is an estrogen receptor modulator and is a postoperative adjuvant therapy mainly for patients with ER/PR receptor-positive breast cancer. The expression of circTRIM28¹⁰¹ and circ_UBE2D2¹⁰² was significantly increased in tamoxifen-resistant tissues, and the expression of circ_UBE2D2 was also increased in exosomes derived from breast cancer resistant cells.

Trastuzumab significantly improves the prognosis of HER2 positive breast cancer patients, and consequently, trastuzumab resistance greatly hinders the treatment of HER2 positive breast cancer patients. Circ- β -TrCP was significantly increased in the serum of trastuzumab resistant subjects, and the circ- β -TrCP derived β -TrCP-343aa protein promoted trastuzumab resistance by elevating expression of NRF2 and antioxidant genes.¹⁰³ Circ-BGN¹⁰⁴ and circCDYL2⁶⁴ were significantly overexpressed in trastuzumab resistant tissues, and HER2-positive patients with high circCDYL2 expression had a higher recurrence rate after trastuzumab treatment.⁶⁴

Conclusion and Prospect

The incidence of breast cancer has been increasing year by year, which is a serious threat to women's health. As an emerging class of non-coding RNA, circRNAs with a covalently closed circular structure are more stable than linear RNAs and less susceptible to degradation by nucleases. This makes them more stable in body fluids, and therefore suitable for liquid biopsy. Detecting circRNAs through body fluids is non-invasive, which enhances patient comfort and compliance. Moreover, circRNAs expression is dysregulated in breast cancer, playing a crucial role in the carcinogenesis, progression, and drug resistance of breast cancer through various mechanisms, and thus circRNAs have emerged as promising biomarker candidates for breast cancer diagnosis, prognosis, molecular subtyping, metastasis, and drug resistance.

The clinical application of circRNAs as markers of breast cancer still has several problems. Despite promising results from preclinical and exploratory studies, circRNAs have not been extensively validated in large-scale clinical trials. The insufficient clinical validation hinders their translation into routine clinical practice for breast cancer diagnosis, prognosis, and monitoring treatment responses. More large-scale clinical trials are needed to validate their sensitivity, specificity, and reliability. Another limitation is that circRNAs detection is costly and not fully standardized, and there may be consistency issues in results between different laboratories. This requires further technical optimization and the establishment of standardized protocols. Moreover, the functional role of specific circRNAs in breast cancer remains largely unexplored. While some circRNAs have been implicated in key oncogenic processes, the exact mechanisms through which they influence tumor behavior and treatment responses are not yet fully understood. In the future, more active research should be carried out on more precise mechanisms of circRNAs in breast cancer.

Additionally, the ideal diagnostic strategy is often multimodal, combining various methods to enhance accuracy. For example, circRNAs can be used in conjunction with mammography and other imaging techniques (such as ultrasound and mammography) to provide a more comprehensive diagnostic picture. CircRNAs have shown immense potential as biomarkers in breast cancer, and their further exploration in clinical trials and other applications will be essential to fully realize their value in the future.

At present, many efforts have been made to address these challenges, such as the emergence of new, highly sensitive detection methods. For example, a small number of clinical samples indicate that, different from quantitative polymerase chain reaction (qPCR), the tetrahedral DNA framework (TDF) sensor does not require an additional target amplification step involving multiple enzymes and procedures. Therefore, it exhibits the advantages of simplicity, ease of operation and versatility, and is expected to become a new detection method.¹⁰⁵ Some circRNAs have entered clinical trials, and it is expected that their unique diagnostic and therapeutic value will be seen in clinical practice in the future. The ongoing clinical trials and studies will help to further explore their clinical applicability and validation. For instance, hsa_circ_0001785 and hsa_circ_100219 may potentially be used as diagnostic and prognostic biomarkers for human breast cancer in the future (NCT05771337, <https://clinicaltrials.gov/study/NCT05771337>). Furthermore, with the emerging functions and mechanisms of circRNAs in breast cancer, they can not only serve as biomarkers but also as therapeutic targets. For example, anti-sense oligonucleotide (ASO)-targeting circPVT1 inhibits ER α -positive breast cancer cell and tumor growth, re-sensitizing tamoxifen-resistant ER α -positive breast cancer cells to tamoxifen treatment. Thus, circPVT1 may serve as a diagnostic biomarker and therapeutic target for ER α -positive breast cancer in the clinic.¹⁰⁶ Recent studies highlighted the therapeutic potential of exploiting tumour-specific circRNAs in the development of effective antigen-based cancer vaccines, including peptide vaccines and circRNA vaccines. It suggests that vaccination utilizing tumour-specific circRNAs may serve as an immunotherapeutic strategy against malignant tumours.¹⁰⁷ Currently, research on the circFAM53B-219aa dendritic cell vaccine treatment has entered clinical trials (NCT06530082, <https://clinicaltrials.gov/study/NCT06530082>).

In conclusion, more and more studies have shown the value of circRNAs as tumor biomarkers and potential therapeutic targets. This review focuses on the role of circRNAs as tumor biomarkers in breast cancer diagnosis, prognosis, molecular types, metastasis and drug resistance, highlighting the significant implications for future circRNAs research. Although further research is needed, the promise of circRNAs as tumor biomarkers for breast cancer is promising.

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YW and KZ conceived the idea. LX, YH, LD, ZQ, SC, and YD searched the literature, designed and draw all the figure and tables. YW and KZ supervised the whole work and revised the manuscript. LX and YH wrote the paper. All authors read and approved the final manuscript.

Consent to Participate

Not applicable.

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Not applicable.

Data Availability

Since this is a review article, there are no new datasets generated or analyzed. All relevant data and information cited in this review are available in the original research articles referenced throughout the manuscript. For any additional inquiries or access to specific data sets, readers are encouraged to refer to the cited studies.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Considerations

Not applicable.

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References

- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024; 74(3):229–263. doi:10.3322/caac.21834.
- Wang H, Xiao Y, Wu L, Ma D. Comprehensive circular RNA profiling reveals the regulatory role of the circRNA-000911/miR-449a pathway in breast carcinogenesis. *Int J Oncol.* 2018;52(3):743–754. doi:10.3892/ijo.2018.4265.
- Harjes U. Breast cancer: Staying silent. *Nat Rev Cancer.* 2018; 18(3):136. doi:10.1038/nrc.2018.17.
- Rodgers RJ, Reid GD, Koch J, et al. The safety and efficacy of controlled ovarian hyperstimulation for fertility preservation in women with early breast cancer: A systematic review. *Hum Reprod.* 2017;32(5):1033–1045. doi:10.1093/humrep/dex027.
- Jafari SH, Saadatpour Z, Salmaninejad A, et al. Breast cancer diagnosis: Imaging techniques and biochemical markers. *J Cell Physiol.* 2018;233(7):5200–5213. doi:10.1002/jcp.26379.
- Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin.* 2019; 69(5):363–385. doi:10.3322/caac.21565.
- Andre F, Filleron T, Kamal M, et al. Genomics to select treatment for patients with metastatic breast cancer. *Nature.* 2022; 610(7931):343–348. doi:10.1038/s41586-022-05068-3.
- Yin Y, Yan Y, Fan B, et al. Novel combination therapy for triple-negative breast cancer based on an intelligent hollow carbon sphere. *Research (Wash D C).* 2023;6:0098. doi:10.34133/research.0098.
- Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol.* 2010;28(20): 3271–3277. doi:10.1200/jco.2009.25.9820.
- Nemeth K, Bayraktar R, Ferracin M, Calin GA. Non-coding RNAs in disease: From mechanisms to therapeutics. *Nat Rev Genet.* 2024;25(3):211–232. doi:10.1038/s41576-023-00662-1.
- Lin X, Wu Z, Hu H, Luo ML, Song E. Non-coding RNAs rewire cancer metabolism networks. *Semin Cancer Biol.* 2021; 75:116–126. doi:10.1016/j.semcancer.2020.12.019.
- Hashimoto K, Ochiya T, Shimomura A. Liquid biopsy using non-coding RNAs and extracellular vesicles for breast cancer management. *Breast Cancer (Tokyo, Japan).* 2025;32(1): 16–25. doi:10.1007/s12282-024-01562-w.
- Tiwari A, Mukherjee B, Dixit M. MicroRNA key to angiogenesis regulation: MiRNA biology and therapy. *Curr Cancer Drug Targets.* 2018;18(3):266–277. doi:10.2174/1568009617666170630142725.
- Peng J, Lin Y, Sheng X, et al. Serum miRNA-1 may serve as a promising noninvasive biomarker for predicting treatment response in breast cancer patients receiving neoadjuvant chemotherapy. *BMC cancer.* 2024;24(1):789. doi:10.1186/s12885-024-12500-6.
- Xu S, Wang L, Zhao Y, et al. Metabolism-regulating non-coding RNAs in breast cancer: Roles, mechanisms and clinical applications. *J Biomed Sci.* 2024;31(1):25. doi:10.1186/s12929-024-01013-w.
- Lan F, Zhang X, Li H, Yue X, Sun Q. Serum exosomal lncRNA XIST is a potential non-invasive biomarker to diagnose recurrence of triple-negative breast cancer. *J Cell Mol Med.* 2021; 25(16):7602–7607. doi:10.1111/jcmm.16009.
- Elango R, Radhakrishnan V, Rashid S, et al. Long noncoding RNA profiling unveils LINC00960 as unfavorable prognostic biomarker promoting triple negative breast cancer progression. *Cell Death Discov.* 2024;10(1):333. doi:10.1038/s41420-024-02091-3.
- Hentze MW, Preiss T. Circular RNAs: Splicing's enigma variations. *Embo J.* 2013;32(7):923–925. doi:10.1038/emboj.2013.53.
- Wilusz JE, Sharp PA. Molecular biology. A circuitous route to noncoding RNA. *Science.* 2013;340(6131):440–441. doi:10.1126/science.1238522.

20. Li F, Yang Q, He AT, Yang BB. Circular RNAs in cancer: Limitations in functional studies and diagnostic potential. *Semin Cancer Biol.* 2021;75:49–61. doi:10.1016/j.semcancer.2020.10.002.
21. Conn VM, Chinnaiyan AM, Conn SJ. Circular RNA in cancer. *Nat Rev Cancer.* 2024;24(9):597–613. doi:10.1038/s41568-024-00721-7.
22. Fang L, Zhu Z, Han M, Li S, Kong X, Yang L. Unlocking the potential of extracellular vesicle circRNAs in breast cancer: From molecular mechanisms to therapeutic horizons. *Biomed Pharmacother.* 2024;180:117480. doi:10.1016/j.biopha.2024.117480.
23. Xu A, Zhu L, Yao C, Zhou W, Guan Z. The therapeutic potential of circular RNA in triple-negative breast cancer. *Cancer Drug Resistance (Alhambra, Calif.)*. 2024;7:13. doi:10.20517/cdr.2023.141.
24. Liu Y, Ma L, Hua F, et al. Exosomal circCARM1 from spheroids reprograms cell metabolism by regulating PFKFB2 in breast cancer. *Oncogene.* 2022;41(14):2012–2025. doi:10.1038/s41388-021-02061-4.
25. Liang L, Gao M, Li W, et al. CircGSK3 β mediates PD-L1 transcription through miR-338-3p/PRMT5/H3K4me3 to promote breast cancer cell immune evasion and tumor progression. *Cell Death Discov.* 2024;10(1):426. doi:10.1038/s41420-024-02197-8.
26. Cai F, Fu W, Tang L, et al. Hsa_circ_0000515 is a novel circular RNA implicated in the development of breast cancer through its regulation of the microRNA-296-5p/CXCL10 axis. *FEBS J.* 2021;288(3):861–883. doi:10.1111/febs.15373.
27. Liu P, Wang Z, Ou X, et al. The FUS/circEZH2/KLF5/ feedback loop contributes to CXCR4-induced liver metastasis of breast cancer by enhancing epithelial-mesenchymal transition. *Mol Cancer.* 2022;21(1):198. doi:10.1186/s12943-022-01653-2.
28. Tran AM, Chalbatani GM, Berland L, et al. A new world of biomarkers and therapeutics for female reproductive system and breast cancers: Circular RNAs. *Front Cell Dev Biol.* 2020;8:50. doi:10.3389/fcell.2020.00050.
29. Ameli-Mojarad M, Ameli-Mojarad M, Nourbakhsh M, Nazemalhosseini-Mojarad E. Circular RNA hsa_circ_0005046 and hsa_circ_0001791 may become diagnostic biomarkers for breast cancer early detection. *J Oncol.* 2021;2021:2303946. doi:10.1155/2021/2303946.
30. Jia Q, Ye L, Xu S, et al. Circular RNA 0007255 regulates the progression of breast cancer through miR-335-5p/SIX2 axis. *Thorac Cancer.* 2020;11(3):619–630. doi:10.1111/1759-7714.13306.
31. Ding L, Xie Z. CircWHSC1 regulates malignancy and glycolysis by the miR-212-5p/AKT3 pathway in triple-negative breast cancer. *Exp Mol Pathol.* 2021;123:104704. doi:10.1016/j.yexmp.2021.104704.
32. Chen H, Wang X, Cheng H, Deng Y, Chen J, Wang B. CircRNA circRREB1 promotes tumorigenesis and progression of breast cancer by activating Erk1/2 signaling through interacting with GNB4. *Heliyon.* 2024;10(7):e28785. doi:10.1016/j.heliyon.2024.e28785.
33. Abtin M, Nafisi N, Hosseinzadeh A, et al. Inhibition of breast cancer cell growth and migration through siRNA-mediated modulation of circ_0009910/miR-145-5p/MUC1 axis. *Noncoding RNA Res.* 2024;9(2):367–375. doi:10.1016/j.nrna.2024.01.016.
34. Zhang F, Wei D, Xie S, et al. CircZCCHC2 decreases pirarubicin sensitivity and promotes triple-negative breast cancer development via the miR-1200/TPR axis. *iScience.* 2024;27(3):109057. doi:10.1016/j.isci.2024.109057.
35. Song R, Guo P, Ren X, et al. A novel polypeptide CAPG-171aa encoded by circCAPG plays a critical role in triple-negative breast cancer. *Mol Cancer.* 2023;22(1):104. doi:10.1186/s12943-023-01806-x.
36. Wang B, Chen H, Deng Y, et al. CircDNAJC11 interacts with TAF15 to promote breast cancer progression via enhancing MAPK6 expression and activating the MAPK signaling pathway. *J Transl Med.* 2023;21(1):186. doi:10.1186/s12967-023-04020-x.
37. Chen H, Yang R, Xing L, et al. Hypoxia-inducible CircPFKFB4 promotes breast cancer progression by facilitating the CRL4(DDB2) E3 ubiquitin ligase-mediated p27 degradation. *Int J Biol Sci.* 2022;18(9):3888–3907. doi:10.7150/ijbs.72842.
38. Li Z, Chen Z, Hu G, et al. Profiling and integrated analysis of differentially expressed circRNAs as novel biomarkers for breast cancer. *J Cell Physiol.* 2020;235(11):7945–7959. doi:10.1002/jcp.29449.
39. Li X, Zhang D, Feng Z, et al. Circular RNA circPRMT5 is upregulated in breast cancer and is required for cell proliferation and migration. *Turk J Med Sci.* 2022;52(2):303–312. doi:10.55730/1300-0144.5316.
40. Omid-Shafaat R, Moayeri H, Rahimi K, et al. Serum circ-FAF1/circ-ELP3: A novel potential biomarker for breast cancer diagnosis. *J Clin Lab Anal.* 2021;35(11):e24008. doi:10.1002/jcla.24008.
41. Wang YW, Xu Y, Wang YY, et al. Elevated circRNAs circ_0000745, circ_0001531 and circ_0001640 in human whole blood: Potential novel diagnostic biomarkers for breast cancer. *Exp Mol Pathol.* 2021;121:104661. doi:10.1016/j.yexmp.2021.104661.
42. Lü L, Sun J, Shi P, et al. Identification of circular RNAs as a promising new class of diagnostic biomarkers for human breast cancer. *Oncotarget.* 2017;8(27):44096–44107. doi:10.18632/oncotarget.17307.
43. Song X, Liang Y, Sang Y, et al. circHMCU promotes proliferation and metastasis of breast cancer by sponging the let-7 family. *Mol Ther Nucleic Acids.* 2020;20:518–533. doi:10.1016/j.omtn.2020.03.014.
44. Liang Y, Ye F, Luo D, et al. Exosomal circSIPA1L3-mediated intercellular communication contributes to glucose metabolic reprogramming and progression of triple negative breast cancer. *Mol Cancer.* 2024;23(1):125. doi:10.1186/s12943-024-02037-4.
45. Chen C, Lu J, Li W, Lu X. Circular RNA ATP2C1 (has_circ_0005797) sponges miR-432/miR-335 to promote breast cancer progression through regulating CCND1 expression. *Am J Cancer Res.* 2023;13(8):3433–3448.
46. Wang G, Qian M, Jian W, Chu J, Huang Y. Has_circ_0000069 expression in breast cancer and its influences on prognosis and

- cellular activities. *Oncol Res.* 2023;31(1):63–70. doi:10.32604/or.2022.028168.
47. Yang L, Chen Y. Circ_0008717 sponges miR-326 to elevate GATA6 expression to promote breast cancer tumorigenicity. *Biochem Genet.* 2023;61(2):578–596. doi:10.1007/s10528-022-10270-z.
 48. Wang M, Chen D, Zhang H, Luo C. Circular RNA circPTK2 modulates migration and invasion via miR-136/NFIB signaling on triple-negative breast cancer cells in vitro. *Inflamm Res.* 2022; 71(4):409–421. doi:10.1007/s00011-022-01548-4.
 49. Li Y, Wang Z, Su P, et al. circ-EIF6 encodes EIF6-224aa to promote TNBC progression via stabilizing MYH9 and activating the wnt/beta-catenin pathway. *Mol Ther.* 2022;30(1):415–430. doi:10.1016/j.ymthe.2021.08.026.
 50. Long T, Tan M. To investigate the role and potential mechanism of has_circ_RBMS3 in bone metastasis of breast cancer based on bioinformatics. *Cell Biochem Biophys.* 2024. doi:10.1007/s12013-024-01332-7
 51. Zeng K, He B, Yang BB, et al. The pro-metastasis effect of circANKS1B in breast cancer. *Mol Cancer.* 2018;17(1):160. doi:10.1186/s12943-018-0914-x.
 52. Wang X, Chen T, Li C, et al. CircRNA-CREIT inhibits stress granule assembly and overcomes doxorubicin resistance in TNBC by destabilizing PKR. *J Hematol Oncol.* 2022;15(1): 122. doi:10.1186/s13045-022-01345-w.
 53. Du C, Zhang J, Zhang L, Zhang Y, Wang Y, Li J. Hsa_circRNA_102229 facilitates the progression of triple-negative breast cancer via regulating the miR-152-3p/PFTK1 pathway. *J Gene Med.* 2021;23(9):e3365. doi:10.1002/jgm.3365.
 54. Liu J, Kong L, Bian W, Lin X, Wei F, Chu J. circRNA_0001006 predicts prognosis and regulates cellular processes of triple-negative breast cancer via miR-424-5p. *Cell Div.* 2023;18(1): 7. doi:10.1186/s13008-023-00089-4.
 55. Liu Y, Liu Y, He Y, et al. Hypoxia-Induced FUS-circTBC1D14 stress granules promote autophagy in TNBC. *Adv Sci (Weinh).* 2023;10(10):e2204988. doi:10.1002/advs.202204988.
 56. Wang L, Zhou Y, Jiang L, et al. CircWAC induces chemotherapeutic resistance in triple-negative breast cancer by targeting miR-142, upregulating WWP1 and activating the PI3K/AKT pathway. *Mol Cancer.* 2021;20(1):43. doi:10.1186/s12943-021-01332-8.
 57. Yang R, Chen H, Xing L, et al. Hypoxia-induced circWSB1 promotes breast cancer progression through destabilizing p53 by interacting with USP10. *Mol Cancer.* 2022;21(1):88. doi:10.1186/s12943-022-01567-z.
 58. Darbeheshti F, Zokaie E, Mansoori Y, et al. Circular RNA hsa_circ_0044234 as distinct molecular signature of triple negative breast cancer: A potential regulator of GATA3. *Cancer Cell Int.* 2021;21(1):312. doi:10.1186/s12935-021-02015-6.
 59. Liu Z, Zhou Y, Liang G, et al. Circular RNA hsa_circ_001783 regulates breast cancer progression via sponging miR-200c-3p. *Cell Death Dis.* 2019;10(2):55. doi:10.1038/s41419-018-1287-1.
 60. Liang G, Ling Y, Mehrpour M, et al. Autophagy-associated circRNA circCDYL augments autophagy and promotes breast cancer progression. *Mol Cancer.* 2020;19(1):65. doi:10.1186/s12943-020-01152-2.
 61. Shao G, Fan X, Zhang P, Liu X, Huang L, Ji S. Circ_0004676 exacerbates triple-negative breast cancer progression through regulation of the miR-377-3p/E2F6/PNO1 axis. *Cell Biol Toxicol.* 2023;39(5):2183–2205. doi:10.1007/s10565-022-09704-6.
 62. Li J, Dong X, Kong X, et al. Circular RNA hsa_circ_0067842 facilitates tumor metastasis and immune escape in breast cancer through HuR/CMTM6/PD-L1 axis. *Biol Direct.* 2023;18(1):48. doi:10.1186/s13062-023-00397-3.
 63. Zhang X, Su X, Guo Z, Jiang X, Li X. Circular RNA La-related RNA-binding protein 4 correlates with reduced tumor stage, as well as better prognosis, and promotes chemosensitivity to doxorubicin in breast cancer. *J Clin Lab Anal.* 2020;34(7): e23272. doi:10.1002/jcla.23272.
 64. Ling Y, Liang G, Lin Q, et al. circCDYL2 promotes trastuzumab resistance via sustaining HER2 downstream signaling in breast cancer. *Mol Cancer.* 2022;21(1):8. doi:10.1186/s12943-021-01476-7.
 65. Gao D, Qi X, Zhang X, Fang K, Guo Z, Li L. Hsa_circRNA_0006528 as a competing endogenous RNA promotes human breast cancer progression by sponging miR-7-5p and activating the MAPK/ERK signaling pathway. *Mol Carcinog.* 2019;58(4):554–564. doi:10.1002/mc.22950.
 66. Zhou B, Xue J, Wu R, et al. CREBZF mRNA nanoparticles suppress breast cancer progression through a positive feedback loop boosted by circPAPD4. *J Exp Clin Cancer Res.* 2023;42(1):138. doi:10.1186/s13046-023-02701-5.
 67. Geng Z, Wang W, Chen H, Mao J, Li Z, Zhou J. Circ_0001667 promotes breast cancer cell proliferation and survival via hippo signal pathway by regulating TAZ. *Cell Biosci.* 2019;9:104. doi: 10.1186/s13578-019-0359-y.
 68. Huang S, Xie J, Lei S, Fan P, Zhang C, Huang Z. CircDUSP1 regulates tumor growth, metastasis, and paclitaxel sensitivity in triple-negative breast cancer by targeting miR-761/DACT2 signaling axis. *Mol Carcinog.* 2023;62(4):450–463. doi:10.1002/mc.23498.
 69. Venkitaraman R. Triple-negative/basal-like breast cancer: Clinical, pathologic and molecular features. *Expert Rev Anticancer Ther.* 2010;10(2):199–207. doi:10.1586/era.09.189.
 70. Green-Tripp G, Nattress C, Halldén G. Targeting triple negative breast cancer with oncolytic adenoviruses. *Front Mol Biosci.* 2022;9:901392. doi:10.3389/fmolb.2022.901392.
 71. Boyle P. Triple-negative breast cancer: Epidemiological considerations and recommendations. *Ann Oncol.* 2012;23(Suppl 6): vi7–v12. doi:10.1093/annonc/mds187
 72. Asano T. Drug resistance in cancer therapy and the role of epigenetics. *J Nippon Med Sch.* 2020;87(5):244–251. doi:10.1272/jnms.JNMS.2020_87-508.
 73. Kristensen LS, Hansen TB, Venø MT, Kjems J. Circular RNAs in cancer: Opportunities and challenges in the field. *Oncogene.* 2018;37(5):555–565. doi:10.1038/onc.2017.361.
 74. Shi Y, Han T, Liu C. CircRNA hsa_circ_0006220 acts as a tumor suppressor gene by regulating miR-197-5p/CDH19 in triple-negative breast cancer. *Ann Transl Med.* 2021;9(15): 1236. doi:10.21037/atm-21-2934.
 75. Chen D, Zeng S, Qiu H, et al. Circ-FOXO3 inhibits triple-negative breast cancer growth and metastasis via regulating

- WHSC1-H3K36me2-Zeb2 axis. *Cell Signal.* 2024;117:111079. doi:10.1016/j.cellsig.2024.111079.
76. Fan Y, Wang J, Jin W, et al. CircNR3C2 promotes HRD1-mediated tumor-suppressive effect via sponging miR-513a-3p in triple-negative breast cancer. *Mol Cancer.* 2021;20(1):25. doi:10.1186/s12943-021-01321-x.
 77. Darbeheshti F, Mansoori Y, Azizi-Tabesh G, et al. Evaluation of circ_0000977-mediated regulatory network in breast cancer: A potential discriminative biomarker for triple-negative tumors. *Biochem Genet.* 2023;61(4):1487–1508. doi:10.1007/s10528-023-10331-x.
 78. Li J, Gao X, Zhang Z, et al. CircCD44 plays oncogenic roles in triple-negative breast cancer by modulating the miR-502-5p/KRAS and IGF2BP2/Myc axes. *Mol Cancer.* 2021;20(1):138. doi:10.1186/s12943-021-01444-1.
 79. Lan J, Wang L, Cao J, Wan Y, Zhou Y. circBRAF promotes the progression of triple-negative breast cancer through modulating methylation by recruiting KDM4B to histone H3K9me3 and IGF2BP3 to mRNA. *Am J Cancer Res.* 2024;14(5):2020–2036. doi:10.62347/oolog5765.
 80. Zhang C, Yu Z, Yang S, et al. ZNF460-mediated circRPPH1 promotes TNBC progression through ITGA5-induced FAK/PI3K/AKT activation in a ceRNA manner. *Mol Cancer.* 2024;23(1):33. doi:10.1186/s12943-024-01944-w.
 81. Wang YW, Chen X, Tian Y, Liu L, Su P. Decreased expression of circ_0000160 in breast cancer with axillary lymph node metastasis. *Front Mol Biosci.* 2021;8:690826. doi:10.3389/fmolb.2021.690826.
 82. Yu Y, Zheng W, Ji C, et al. Tumor-derived circRNAs as circulating biomarkers for breast cancer. *Front Pharmacol.* 2022;13:811856. doi:10.3389/fphar.2022.811856.
 83. Chen Q, Yang Z, Ding H, Li H, Wang W, Pan Z. CircWHSC1 promotes breast cancer progression by regulating the FASN/AMPK/mTOR axis through sponging miR-195-5p. *Front Oncol.* 2021;11:649242. doi:10.3389/fonc.2021.649242.
 84. Song H, Zhao Z, Ma L, Zhao W, Hu Y, Song Y. Novel exosomal circEGFR facilitates triple negative breast cancer autophagy via promoting TFEB nuclear trafficking and modulating miR-224-5p/ATG13/ULK1 feedback loop. *Oncogene.* 2024;43(11):821–836. doi:10.1038/s41388-024-02950-4.
 85. Fu B, Liu W, Zhu C, et al. Circular RNA circBCBM1 promotes breast cancer brain metastasis by modulating miR-125a/BRD4 axis. *Int J Biol Sci.* 2021;17(12):3104–3117. doi:10.7150/ijbs.58916.
 86. Xu Y, Li X, Zhang S, et al. CircMMP2(6,7) cooperates with β -catenin and PRMT5 to disrupt bone homeostasis and promote breast cancer bone metastasis. *Cancer Res.* 2024;84(2):328–343. doi:10.1158/0008-5472.Can-23-1899.
 87. Wu S, Lu J, Zhu H, et al. A novel axis of circKIF4A-miR-637-STAT3 promotes brain metastasis in triple-negative breast cancer. *Cancer Lett.* 2024;581:216508. doi:10.1016/j.canlet.2023.216508.
 88. Wang Z, Yang L, Wu P, et al. The circROBO1/KLF5/FUS feedback loop regulates the liver metastasis of breast cancer by inhibiting the selective autophagy of afadin. *Mol Cancer.* 2022;21(1):29. doi:10.1186/s12943-022-01498-9.
 89. Zeng Y, Du W, Huang Z, et al. Hsa_circ_0060467 promotes breast cancer liver metastasis by complexing with eIF4A3 and sponging miR-1205. *Cell Death Discov.* 2023;9(1):153. doi:10.1038/s41420-023-01448-4.
 90. Zhang Y, Tan Y, Yuan J, et al. circLIFR-007 reduces liver metastasis via promoting hnRNPA1 nuclear export and YAP phosphorylation in breast cancer. *Cancer Lett.* 2024;592:216907. doi:10.1016/j.canlet.2024.216907.
 91. Hao J, Du X, Lv F, Shi Q. Knockdown of circ_0006528 suppresses cell proliferation, migration, invasion, and Adriamycin chemoresistance via regulating the miR-1236-3p/CHD4 axis in breast cancer. *J Surg Res.* 2021;260:104–115. doi:10.1016/j.jss.2020.10.031.
 92. Cui Y, Fan J, Shi W, Zhou Z. Circ_0001667 knockdown blocks cancer progression and attenuates Adriamycin resistance by depleting NCOA3 via releasing miR-4458 in breast cancer. *Drug Dev Res.* 2022;83(1):75–87. doi:10.1002/ddr.21845.
 93. Chen JJ, Shi P, Cui ZC, Jiang N, Ma J. CircRNA_0044556 affects the sensitivity of triple-negative breast cancer cells to paclitaxel by regulating miR-665. *J Chemother.* 2024:1–9. doi:10.1080/1120009x.2024.2345028.
 94. Wang H, Shan S, Wang H, Wang X. CircATXN7 contributes to the progression and doxorubicin resistance of breast cancer via modulating miR-149-5p/HOXA11 pathway. *Anticancer Drugs.* 2022;33(1):e700–e710. doi:10.1097/cad.0000000000001243.
 95. Pallis AG, Boukovinas I, Ardavanis A, et al. A multicenter randomized phase III trial of vinorelbine/gemcitabine doublet versus capecitabine monotherapy in anthracycline- and taxane-pretreated women with metastatic breast cancer. *Ann Oncol.* 2012;23(5):1164–1169. doi:10.1093/annonc/mdr405.
 96. Seo JH, Oh SC, Choi CW, et al. Phase II study of a gemcitabine and cisplatin combination regimen in taxane resistant metastatic breast cancer. *Cancer Chemother Pharmacol.* 2007;59(2):269–274. doi:10.1007/s00280-006-0266-x.
 97. Zang H, Li Y, Zhang X, Huang G. Circ-RNF111 contributes to paclitaxel resistance in breast cancer by elevating E2F3 expression via miR-140-5p. *Thorac Cancer.* 2020;11(7):1891–1903. doi:10.1111/1759-7714.13475.
 98. Kong Z, Han Q, Zhu B, Wan L, Feng E. Circ_0069094 regulates malignant phenotype and paclitaxel resistance in breast cancer cells via targeting the miR-136-5p/YWHAZ axis. *Thorac Cancer.* 2023;14(19):1831–1842. doi:10.1111/1759-7714.14928.
 99. Yang W, Gong P, Yang Y, Yang C, Yang B, Ren L. Circ-ABCB10 contributes to paclitaxel resistance in breast cancer through let-7a-5p/DUSP7 axis. *Cancer Manag Res.* 2020;12:2327–2337. doi:10.2147/cmar.S238513.
 100. Liu J, Kong L, Bian W, Lin X, Wei F, Chu J. CircRNA CircABCB1 diminishes the sensitivity of breast cancer cells to docetaxel by sponging MiR-153-3p. *Tohoku J Exp Med.* 2023;261(1):25–33. doi:10.1620/tjem.2023.J039.
 101. Yang S, Zou C, Li Y, et al. Knockdown circTRIM28 enhances tamoxifen sensitivity via the miR-409-3p/HMGA2 axis in breast cancer. *Reprod Biol Endocrinol.* 2022;20(1):146. doi:10.1186/s12958-022-01011-3.
 102. Hu K, Liu X, Li Y, et al. Exosomes mediated transfer of circ_UBE2D2 enhances the resistance of breast cancer to

- tamoxifen by binding to MiR-200a-3p. *Med Sci Monit.* 2020;26:e922253. doi:10.12659/msm.922253.
103. Wang S, Wang Y, Li Q, Li X, Feng X, Zeng K. The novel β -TrCP protein isoform hidden in circular RNA confers trastuzumab resistance in HER2-positive breast cancer. *Redox Biol.* 2023;67:102896. doi:10.1016/j.redox.2023.102896.
104. Wang S, Wang Y, Li Q, Li X, Feng X. A novel circular RNA confers trastuzumab resistance in human epidermal growth factor receptor 2-positive breast cancer through regulating ferroptosis. *Environ Toxicol.* 2022;37(7):1597–1607. doi:10.1002/tox.23509.
105. Zhou Z, Han B, Wang Y, et al. Fast and sensitive multivalent spatial pattern-recognition for circular RNA detection. *Nat Commun.* 2024;15(1):10900. doi:10.1038/s41467-024-55364-x.
106. Yi J, Wang L, Hu GS, et al. CircPVT1 promotes ER-positive breast tumorigenesis and drug resistance by targeting ESR1 and MAVS. *EMBO J.* 2023;42(10):e112408. doi:10.15252/embj.2022112408.
107. Huang D, Zhu X, Ye S, et al. Tumour circular RNAs elicit anti-tumour immunity by encoding cryptic peptides. *Nature.* 2024; 625(7995):593–602. doi:10.1038/s41586-023-06834-7.