Practical Laboratory Medicine 45 (2025) e00470

Contents lists available at ScienceDirect

Practical Laboratory Medicine

journal homepage: www.elsevier.com/locate/plabm

Registered Report Stage II

Evaluation of CircHIPK3 biomarker potential in breast cancer

Ensiyeh Bahadoran [a], Davood Mohammadi [b], Manijeh Jalilvand [a], Sahar Moghbelinejad [a,*]

[a] Cellular and Molecular Research Centre, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran

[b] Department of Surgery, School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran

ARTICLE INFO

Keywords:
Breast cancer
Circular RNA
Biomarker
Liquid biopsy

ABSTRACT

Background: Nowadays, the investigation of circular RNAs (circRNAs) in various cancers is of great interest. In this research, we evaluated circHIPK3 biomarker potential in breast cancer (BC).
Methods: The studied samples were 100 cancer and adjacent normal tissues, plasma from 95 cancer patients, 42 patients with fibroadenomatosis, and 93 healthy donors. Illumina high-throughput Hi Seq 2000 sequencing performed expression profiling on 4 pairs of cancerous and normal breast tissues. For expression confirmation, Quantitative real-time fluorescent polymerase chain reaction (qRT-PCR) was used to detect the expression level of circHIPK3. CircHIPK3 diagnostic efficacy was evaluated by the receiver operating characteristic curve (ROC).
Results: Based on high-throughput sequencing and bioinformatics results circHIPK3 had the highest expression in cancer tissues ($P = 0.00034$). Real-time results showed expression upregulation of circHIPK3 in BC tissues and plasma in comparison to healthy controls ($P < 0.0001$). For diagnostic potential, the area under the curve (AUC) result was 0.8087 (95 % CI: 0.7309 to 0.8866, $P < 0.0001$). Also, our results showed high specificity and sensitivity of circHIPK3 when evaluated alongside the CA-15-3 and CEA. Pathologic criteria evaluation showed that upregulation of circHIPK3 correlates with tumor size.
Conclusions: CircHIPK3 is significantly upregulated in BC tissues and plasma compared to healthy controls, demonstrating high diagnostic potential with an AUC of 0.8087. The expression of circHIPK3 correlates with tumor size, indicating its relevance in the pathologic assessment of BC.

1. Introduction

Breast cancer (BC) presents a major global health challenge as it is the most frequently diagnosed cancer worldwide, with over 2.3 million new cases reported in 2020. It remains the leading cause of cancer-related death among women, with approximately 685,000 fatalities in the same year. More than half of these diagnoses and two-thirds of the deaths occurred in less-developed regions. Projections estimate that by 2040, annual BC cases will surpass 3 million [1,2]. Despite significant advances in treatment, the complexity and heterogeneity of the BC demand the continuous exploration of novel molecular mechanisms. Moreover, early diagnosis is critical for effective treatment and improved prognoses [3,4]. BC screening primarily uses imaging techniques and serum tumor markers;

* Corresponding author. Cellular and Molecular Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences. P.O. Box: 34197-59811, Qazvin, Iran.
E-mail addresses: bahadoran.ensiyeh@gmail.com (E. Bahadoran), d.mohammadi@gmail.com (D. Mohammadi), rahamj7@yahoo.com (M. Jalilvand), smoghbelinejad@qums.ac.ir (S. Moghbelinejad).

https://doi.org/10.1016/j.plabm.2025.e00470
Received 30 September 2024; Received in revised form 14 March 2025; Accepted 20 March 2025
Available online 20 March 2025

however, both have drawbacks, including high costs and limited diagnostic accuracy. Mammography, with a sensitivity of 54–77 %, and laboratory markers including CA 15-3, CEA, and TPS lack reliability, and recent studies have shown mixed results regarding their effectiveness [5,6]. Consequently, there is an urgent need for highly efficient and specific clinical diagnostic biomarkers to enhance early detection and management of BC.

In cancer biology, non-coding RNAs (ncRNAs), particularly circular RNAs (circRNAs), have become important regulators that provide new insights into the complex networks regulating carcinogenesis and metastasis [7–10]. CircRNAs are formed by back-splicing and have covalently closed loops. The closed loop is constructed by joining the 5′ and 3′ ends of an exon or an intron. CircRNAs are often produced from an exon or an intron of the pre-mRNA (gene precursor mRNA). Different circRNA subtypes may be produced by different splicing of pre-mRNA transcript [11,12]. Through post-transcriptional control, circRNA may be able to alter the growth of tumors in human cancer diffusely [13]. CircRNAs are exceptionally durable because of their covalently closed circular shapes, which protects them from exonuclease degradation and make them attractive candidate biomarkers for evaluating prognosis or diagnosing cancer [14]. Many studies have been carried out on the application of circRNAs in BC diagnosis and progression. Accordingly, hsa_circ_0001785, hsa_circ_0008673, hsa_circ_0001785, and hsa_circ_100219 have been proposed as biomarkers for the diagnosis and progression of BC [5,15,16].

The HIPK3 gene's exon 2 splicing results in cirCHIPK3 (hsa_circ_0000284), a protein with 1099 nucleotides in length [17]. Chen et al. claimed that cirCHIPK3 was increased in BC and predicted a poor prognosis by regulating the miR-193a/HMGB1/PI3K/AKT signaling pathway [18]. QI et al. demonstrated that by controlling miR-326, circHIPK3 enhances the growth, migration, and invasion of BC cells [19]. Zhang et al. found that circHIPK3 delivered by exosomes may increase drug-sensitive BC cell resistance to trastuzumab chemoresistance [20]. This study evaluated the potential of cirCHIPK3 as a potential biomarker for the diagnosis and prognosis of BC.

2. Methods

2.1. Samples collections

The Qazvin University of Medical Science Ethics Committee approved this study and informed consent was obtained from each patient. The study protocol conformed to the principles of the Declaration of Helsinki. For this investigation, 100 BC tissues and nearby normal tissues were obtained from Qazvin University of Medical Science's BioBank. Plasma samples were collected from 42 patients with fibroadenomatosis, 95 patients with BC, and 93 age-matched healthy controls. The diagnoses were made and confirmed by clinicians, and none of the patients with BC underwent radiation or chemotherapy. The pathological data of the patients was gathered and their OVARImedical records were thoroughly examined.

2.2. RNA sequencing for circular RNA profiling

In the first stage, we used the mlTRIZOL reagent (Invitrogen) according to the manufacturer's instructions to extract RNA samples from 402 μl of plasma and 792 mg of frozen tissue. Thermo's NanoDrop 2000c was used to assess the quality and quantity of the isolated RNA. A260/A280 ratios greater than two in the RNA samples were chosen for sequencing and quantitative examination. RNase R was used to treat total RNA and improve the purity of the circRNAs. The modified RNA was further subjected to first-strand complementary DNA (cDNA) synthesis using the Revert Aid First Strand cDNA Synthesis Kit (Thermo Scientific, Fermentas). After size-fractionating the RNA samples, 18–30 nt RNA was separated and purified. For cDNA synthesis, 5′ and 3′ adaptor ligations were carried out. PCR conditions for cDNA synthesis were as follows: 98 °C for 10 s and 72 °C for 15 s for 14 cycles. The size (average molecular length) and purity were assessed using an Agilent Technologies 2100 Bioanalyzer, and the concentration was confirmed by quantitative PCR using Eva Green dye (Jena Bioscience). Illumina HiSeq 2000 (Illumina, Inc.) was used for sequencing. Quantitative real-time polymerase chain reaction (qRT-PCR) (rotor gene) was used to investigate circHIPK3 expression. The primer sequences used are listed in Table 1.

In a 72-well optical strip, the reactions were incubated for 15 min at 95 °C (enzyme activation), then for 20 s at 95 °C and 60 s at 60 °C (40 cycles). Every reaction was carried out in triplicate. Following these procedures, triplicate PCRs were used to calculate the mean Ct value. Ct values were employed to assess the circHIPK3 expression levels. The expression value of the mentioned circRNAs relative to the internal control was determined using the $2^{-\triangle Ct}$ method.

Table 1
Primer sequence of studied genes.

Primer	Sequence
Circ HIPK3-divergent-forward	TTCAACATATCTACAATCTCGGT
Circ HIPK3-divergent-reverse	ACCATTCACATAGGTCCGT
Circ HIPK3- forward	TGAGCCAAGATCGTGCTAC
Circ HIPK3- reverse	GGACACCTGGAATCTAATTCTG
GAPDH- forward	GAAGGTGAAGGTCGGAGTC
GAPDH- reverse	GAAGATGGTGATGGGATTTC

2.3. Statistical analysis

GraphPad Prism software (GraphPad PRISMV 8.4 analytical software) was used for statistical analysis. Student's t-test and Pearson's $\chi 2$ test were used to compare data between pairs of groups and to evaluate the clinical pathological variables.

3. Results

3.1. Profiling of circRNAs expression in studied samples

In the profile investigation, four pairs of BC tissues and nearby normal tissues were employed. The findings demonstrated that there was a difference in the expression of 4246 circRNAs between cancerous and healthy tissues. Based on the expression difference multiple >2.0 and $P < 0.05$, 297 circRNAs were elevated in BC tissues. To choose the most highly upregulated circRNAs, several databases, including CircRNA Db, CircBase, and CircBank, were consulted. Table 2 displays a list of the top-upregulated circRNAs. Of all circRNAs, CircHIPK3 received the highest score; hence, it was chosen for additional analysis.

3.2. CircHIPK3 expression confirmation by real-time PCR

In the examined cancer tissues, upregulation of circHIPK3 was verified ($P < 0.0001$) (Fig. 1a). Furthermore, we found that this circular RNA was significantly overexpressed in the plasma samples of BC patients compared to that in controls and those with fibroadenomatosis ($P < 0.0001$). There was no significant difference between the fibroadenomatosis and control groups ($P = 0.421$) (Fig. 1b). We examined the expression of circHIPK3 in the patients following surgery to provide additional validation. The findings indicated significant underexpression of circular RNA in these patients and significant overexpression following cancer recurrence ($P < 0.001$). Pearson's correlation analysis showed a significant positive correlation between the expression in tissue and plasma samples ($R^2 = 0.764$, $P < 0.001$) (Fig. 2).

3.3. Diagnostic potential of CircHIPK3

The diagnostic potential of circ-RNA was evaluated using the receiver operating characteristic curve (ROC) and area under the curve (AUC) in plasma samples of 95 patients and 93 age-matched controls. The results showed that the plasma level of circHIPK3 could differentiate primary BC patients from controls, with an AUC of 0.8087 (95 % CI: 0.7309–0.8866, $P < 0.0001$) (Fig. 3). In another section of the study, we compared the sensitivity and specificity of circHIPK3 with CA-15-3 and CEA. Results showed that circHIPK3 evaluation in side CA-15-3 and CEA increased the sensitivity and specificity of detection (Table 3).

Clinicopathological evaluation of BC patients showed that the high expression level of circHIPK3 was associated with tumor size ($P = 0.0012$) (Table 4).

4. Discussion

BC is a heterogeneous disease both clinically and molecularly [21]. In the past, the prognosis of BC was determined based on lymph node metastasis, tumor size, and histological tumor grade, which are no longer suitable for early diagnosis of BC [22]. Molecular biomarkers are useful as prognostic and predictive markers, and currently, it is very important to estimate the prognosis of cancer and its targeted treatment [22].

CircRNAs are single-stranded non-coding RNA that are highly abundant in mammalian cells (21–22). Different studies have shown the differential expression of circRNAs in BC and normal non-malignant tissues [23,24]. In recent years, the role of circRNAs in the pathogenesis of BC has received increasing attention. Zheng et al., 2020 reported that circSEPT9 mediated by E2F1 and EIF4A3 facilitates the carcinogenesis and development of triple-negative BC through circSEPT9/miR-637/LIF axis [25]. Zhang et al., 2021 showed that circFOXK2 could act with IGF2BP3, an RNA-binding protein, and miR-370 to synergistically promote BC metastasis [26]. Liu et al., 2022 reported a novel feedback loop, FUS/circEZH2/KLF5/CXCR4, in BC metastasis, and proposed circEZH2 as a novel biomarker and potential target for BC patients' therapy [27]. The role of circRNA circHIPK3 in the pathogenesis of different malignancies has been reported in several studies. Shang et al., 2023 showed serum exosomal circHIPK3 could also be a noninvasive indicator to evaluate cisplatin resistance in gastric cancer [28]. In another study, Liu et al., 2020 reported that circHIPK3 promotes G2/M transition and induces prostate cancer cell proliferation by sponging miR-338-3p and increasing the expression of Cdc25B and Cdc2.

Table 2
Top upregulated circular RNAs in cancerous tissues compared to adjacent normal tissues.

Circ-RNA	Number of reads	$2^{-\Delta ct}$	Adj P-value
CircHIPK3	125.65/353	16.12	0.00034
Circ_001783	678.4/345	12.65	0.000565
CircRNF20	6.435/1.23	8.543	0.00021
CircCER	844.9/1.33	6.432	<0.0001
CircACTN4	124.653/4	3.5632	0.00432

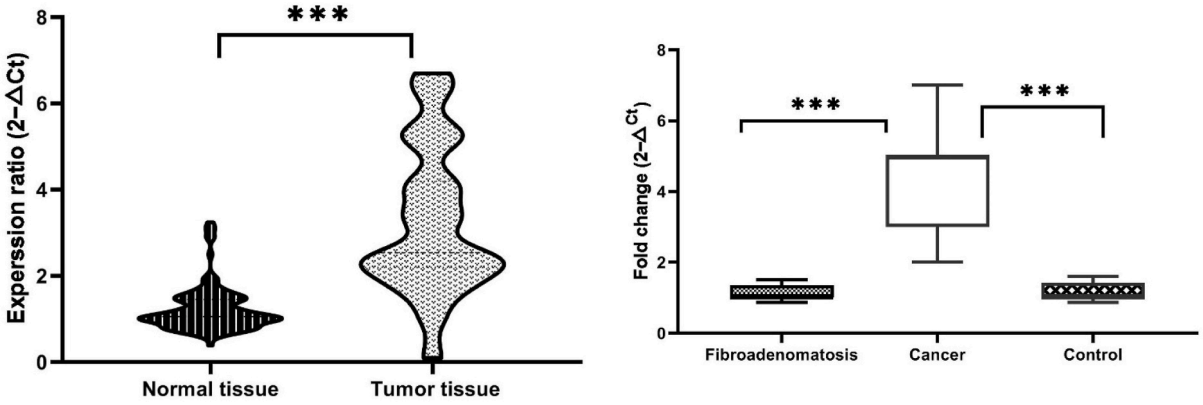

Fig. 1. Overexpression of CircHIPK3 in Breast Cancer Tissues and Plasma Samples. **(a)** overexpression of CircHIPK3 in cancer tissues (3.26 ± 0.167) in comparison to normal tissues (1.22 ± 0.35) ($P < 0.0001$). **(b)** Shows significant overexpression of CircHIPK3 in plasma samples of cancerous patients (4.6 ± 0.97) in comparison to fibroadenomatosis (1.32 ± 0.37), and control patients (1.45 ± 0.18) ($P < 0.0001$).

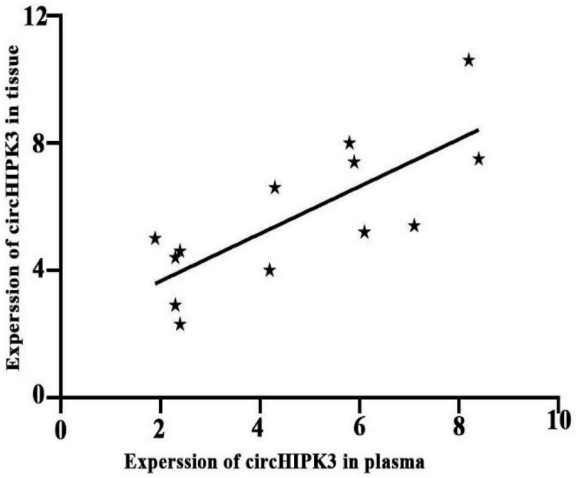

Fig. 2. A positive correlation was observed between the relative expression of circHIPK3 in the plasma and tissues of patients with OC ($R^2 = 0.764$, $P < 0.001$).

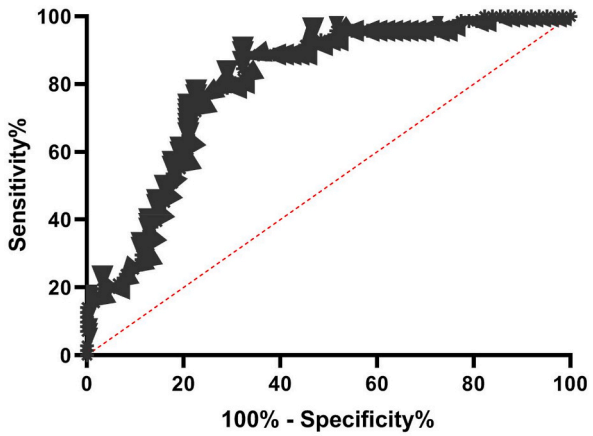

Fig. 3. ROC curve analysis of plasma CircHIPK3 for discriminating primary BC patients from healthy donors showed an AUC of 0.8087 (95 % CI: 0.7309 to 0.8866, $P < 0.0001$).

Table 3
Assessment of the diagnostic values of the combination of CircHIPK3, CA-15-3, and CEA in BC patients and controls. SEN, sensitivity; SPE, specificity; ACCU, overall accuracy; PPV, positive predictive value; NPV, negative predictive value. SEN: sensitivity, SPE: specificity, ACCU: overall accuracy, PPV: positive predictive value, NPV: negative predictive value.

	SEN, %	SPE, %	ACCU, %	PPV, %	NPV, %
CEA	49.4	54.6	66.2	62	63.4
CA-15-3	50.2	66.4	59.3	58	65.4
CircHIPK3	74.4	80.3	79.8	82	84.3
CircHIPK3+ CA-15-3+ CEA	81.8	80.9	79.9	80.5	80.1

Table 4
Correlation between circHIPK3 expression and clinicopathological " parameters. T: refers to the size and extent of the main tumor, TNM: number to describe the tumor (T), node (N), and metastasis (M).

Parameters	circHIPK3expression ratio in tumor = 1 > 1 <1 adj P value			
Gender				
Male	34	7	8	
Female	37	7	6	0.435
Age				
<50	39	5	6	
>50	42	4	3	0.34
Tumor size				
<5 cm	31	**6**	7	
>5 cm	36	**11**	8	**0.0012**
Differentiation				
Well + moderate	26	10	15	
Poor	28	13	12	0.98
T classification				
1–2	30	4	10	
3–4	34	4	9	0.43
Lymph node metastasis				
Positive	31	14	14	
Negative	32	13	14	0.765
TNM stage				
I-II	34	12	13	
III-IV	35	13	12	0.543

CircHIPK3 may play an oncogenic role in prostate cancer [29]. Some reports have described the role of circHIPK3 in the pathogenesis of BC. Lou et al., 2021 introduced circHIPK3 as a novel therapeutic target for treating BC [30]. Qi et al., 2021 showed overexpression of circHIPK3 promoted tumor growth and Ki-67 levels, and inhibited apoptosis [19]. Ni et al., 2021 reported silencing of CircHIPK3 increases sensitivity to the chemotherapy drug [31]. The role of circHIPK3 in angiogenesis and metastasis in BC has also been demonstrated [32]. In 2023 Abdollahi et al. reported the role of circHIPK3 in the radio sensitivity of BC cells [33].

Our RNA sequencing results showed that circHIPK3 had a high score for overexpression, which prompted us to conduct more research on this circRNA. Considering the importance of liquid biopsy in the diagnosis and treatment of BC, the level of expression of this circRNA in the plasma samples of patients was also investigated, and a significant correlation between its expression in tissue and plasma was observed, indicating that cancer tissue cells entered the plasma. Moreover, an increase in the expression of circHIPK3 occurs only in cancerous tissues, but we did not observe this overexpression in fibroadenoma samples, and the expression pattern was similar to that in normal tissues. Another remarkable finding of this study was that the sensitivity and specificity of diagnosis increased when circHIPK3 was combined with other biomarkers (CA-15-3 and CEA). In addition, we observed that circHIPK3 expression was correlated with tumor size. Therefore, circHIPK3 can be used as a diagnostic biomarker in the initiation stage of BC. However, our study didn't show any correlation between circHIPK3 and metastasis or lymph node involvement. In contrast, some other studies have shown its correlation to metastasis in BC by regulating the miR-326 or miR-193a/HMGB1/PI3K/AKT signaling pathway [18,19,30]. The lack of correlation in our study could be due to differences in patient populations, sample sizes, or tumor microenvironment factors. Further research is needed to clarify this difference and determine whether specific subgroups of BC patients exhibit a stronger association between circHIPK3 and metastatic behavior.

Our study highlights the diagnostic potential of circHIPK3 in BC but has some limitations. We did not analyze histopathological subtypes. Additionally, to assess the pure effect of BC, we excluded patients who underwent treatment. Future studies should explore circHIPK3 across subtypes and treatment responses. Moreover, Future research should focus on identifying potential subgroups where circHIPK3 may have a stronger metastatic association. These analyses will provide the prognostic and therapeutic effect of circHIPK3 in BC.

5. Conclusion

In conclusion, this study underscores the significant potential of circHIPK3 as a diagnostic biomarker for BC. The overexpression of circHIPK3 in both tissue and plasma samples of BC patients, along with its correlation with tumor size, highlights its role in early detection. Furthermore, the combination of circHIPK3 with other biomarkers such as CA-15-3 and CEA enhances diagnostic sensitivity and specificity. These findings advocate for the integration of circHIPK3 in clinical diagnostics to improve early detection and management of BC.

CRediT authorship contribution statement

Ensiyeh Bahadoran: Writing – original draft, Methodology. **Davood Mohammadi:** Writing – original draft, Methodology, Data curation. **Manijeh Jalilvand:** Formal analysis. **Sahar Moghbelinejad:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Conceptualization.

Ethics approval

The Ethics Committee of the Qazvin University of Medical Science (IR.QUMS.REC.1400.410) approved this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [S.M], upon reasonable request.

Funding

This work was supported by the Cellular and Molecular Research Center at Qazvin University of Medical Science (Grant number 400000466). Sahar Moghbelinejad has received research support from the Cellular and Molecular Research Center at Qazvin University of Medical Science.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

We appreciate all of the participants in the current study.

Data availability

Data will be made available on request.

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