

ORIGINAL ARTICLE

Relationship of *ITPKA* expression with the prognosis of breast cancer

Jie Zhang^{1*} | Sujie Zhang^{2*} | Xiaoyan Li² | Hongying Pi¹ 

¹Nursing Department, Sixth Medical Center of Chinese PLA Hospital, Medical School of Chinese PLA, Beijing, China

²Department of Oncology, Chinese PLA General Hospital, Medical School of Chinese PLA, Beijing, China

Correspondence

Hongying Pi, Nursing Department, Sixth Medical Center of Chinese PLA Hospital, Medical School of Chinese PLA, Beijing, China.

Email: ergksf@yeah.net

Abstract

Background: Breast cancer (BC) represents a most common cancer among women worldwide. The outcomes of this disease remain dismal due to frequent recurrence and metastasis. Inositol-1,4,5-trisphosphate-3-kinase-A (*ITPKA*) plays an important role in regulating calcium signaling and actin dynamics. The dysregulation of *ITPKA* has been observed in several human cancers. The present study aimed to assess *ITPKA* expression and its prognostic value in BC.

Methods: *ITPKA* expression was examined via quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemistry (IHC) methods. In addition, Kaplan–Meier survival analysis and Cox regression analysis were performed to evaluate prognostic value of *ITPKA* in BC.

Results: Upregulated *ITPKA* expression was found in BC samples, according to both qRT-PCR and IHC analyses (all $p < .05$). *ITPKA* expression was positively correlated with lymph node metastasis ($p = .021$) and TNM stage ($p = .009$). Moreover, BC patients with high expression of *ITPKA* had poor overall survival compared with those with low expression (log-rank $p < .05$). Cox analysis verified that *ITPKA* expression was an independent prognostic factor for BC patients (HR = 4.239, 95%CI = 2.221–8.093 and $p = .000$).

Conclusion: BC cases show increased expression of *ITPKA*. *ITPKA* may act as an independent prognostic biomarker in BC.

KEYWORDS

breast cancer, *ITPKA*, prognosis

1 | INTRODUCTION

Breast cancer (BC) is a prevalent malignancy among women around the world, which results in poor quality of life and high mortality (Ward et al., 2015). The incidence of BC shows an increasing tendency, and about 1, 300, 000

new cases are diagnosed every year worldwide (DeSantis et al., 2014; Kamangar et al., 2006). At early stages, BC patients frequently present the following symptoms: lumps in breast, shape changes in breast and dimpling of skin, or fluid from nipple (Kool et al., 2015). Several risk factors have been associated with the tumorigenesis of BC, such as alcohol, obesity, family history, having children late, and

Jie Zhang and Sujie Zhang co-first authors.

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hormone replacement (McGuire, 2016). The diagnosis and surveillance of BC are mainly dependent on MRI, mammography, thermography, breast specific gamma-camera (BSGC), and ultrasound (Cuk et al., 2013). However, their clinical efficacy is unsatisfactory due to low specificity and sensitivity (Kriege et al., 2004; Saslow et al., 2007; Spanu et al., 2012). Therefore, novel and accurate biomarkers are in urgent need for early screening and prognosis evaluation of BC.

Inositol-1,4,5-trisphosphate-3-kinase-A (*ITPKA*) (OMIM accession number: 147521) is located in 15q15 and encodes a 461 amino acids' polypeptide (Koenig et al., 2015), which has been identified in neurons and testis under physiological conditions (Windhorst et al., 2017). *ITPKA* is one of three recognized inositol trisphosphate 3-kinases (*ITPKs*) which act as catalysts during the phosphorylation of inositol 1,4,5-trisphosphate to inositol 1,3,4,5-tetrakisphosphate, and further regulate calcium signals (Berridge, 1993; Shears, 2004). Besides, *ITPKA* has also been reported to bind to filamentous actin (*F-actin*) so as to manage spine morphology (Johnson & Schell, 2009). In addition, *ITPKA* is involved in the regulation of metastasis and carcinogenesis as well. Dysregulated expression of *ITPKA* has been found in some human cancers, such as oral squamous cell carcinoma, lung cancer, and so on (Kato et al., 2006; Windhorst et al., 2017). However, its role in BC was still unclear.

In this study, we aimed to assess the expression of *ITPKA* in BC tissue samples and to explore its prognostic value in patients with BC.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

Written informed consents were signed by the participants before surgical operation. The current study was approved by the Ethics Committee of Chinese PLA General Hospital.

2.2 | Patients and specimens

BC tissues and adjacent noncancerous tissues were collected from 132 eligible BC patients at Chinese PLA General Hospital. All the tissue specimens were immediately transferred to liquid nitrogen and kept at -80°C for further application. Clinicopathological characteristics of these BC patients were obtained and listed in Table 1, including age, tumor size, lymph node metastasis, the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and TNM stage. All the patients participated in a 5-year follow-up with duration ranging from 6 to 60 months.

TABLE 1 Association of *ITPKA* expression with the clinicopathological features of BC patients

Features	Total no. N = 132	<i>ITPKA</i> ^a expression		p values
		Low (n = 57)	High (n = 75)	
Age (years)				.866
≤50	59	25	34	
>50	73	32	41	
Tumor size (cm)				.700
≤3	60	27	33	
>3	72	30	42	
LN metastasis				.021
Negative	59	32	27	
Positive	73	25	48	
PR expression				.497
Negative	65	30	35	
Positive	67	27	40	
ER expression				.461
Negative	60	28	32	
Positive	72	29	43	
HER-2 expression				.623
Negative	57	26	31	
Positive	75	31	44	
TNM stage				.009
I-II	57	32	25	
III-IV	75	25	50	

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; LN, lymph node; PR, progesterone receptor.

^a*ITPKA* accession number: BC026331.1.

2.3 | RNA extraction and qRT-PCR

Total RNAs were extracted from the prepared tissues using TRIzol reagent (Invitrogen, Life Technologies, Paisley, UK) following the manufacturer's guidelines. The purity of RNA was estimated using the ratio of OD A260/A280, and only RNA samples would be used in subsequent experiments only when their ratio was close to 2.0.

Quantitative real-time polymerase chain reaction (qRT-PCR) method evaluated the mRNA expression of *ITPKA*. The single stranded cDNA was obtained via reverse transcription using PrimeCrip RT Master Mix (Takara, Dalian, China). PCR reaction was carried out utilizing SYBR Green PCR master mix (Applied Biosystems, USA) in Light-Cycler480 384-well PCR system (Roche Diagnostics). *GAPDH* gene was the internal control for *ITPKA*. Primers for *ITPKA* was designed based on GenBank reference sequence (Genebank accession number: BC026331.1). Primer sequences were as follows: *ITPKA* forward: 5'-CCTTCCACCTCGTCGGTCT-3',

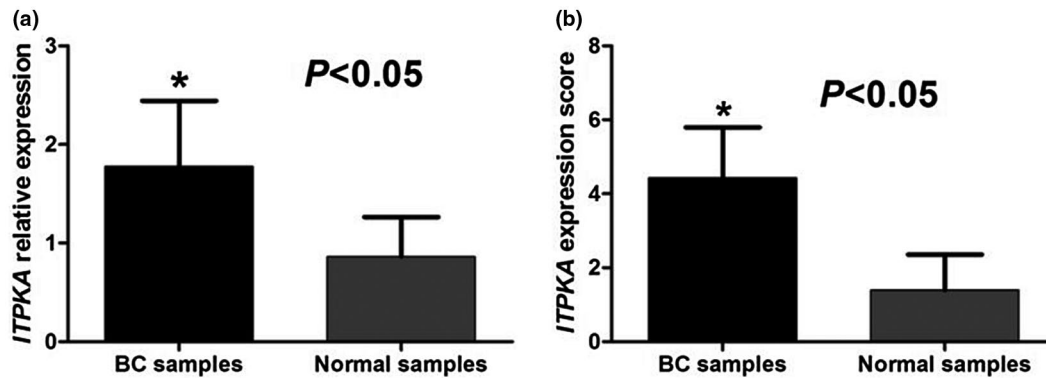


FIGURE 1 Expression of *ITPKA* in BC tissues and paired noncancerous samples. (a) The expression of *ITPKA* mRNA in BC samples and noncancerous samples was measured via qRT-PCR ($p < .05$). (b) The results of IHC analysis for the expression score of *ITPKA* in BC tissues and in matched noncancerous samples ($p < .05$)

reverse: 5'-GCCTTAAACTCCCAGTGTGC-3'; *GAPDH* forward: 5'-GGCCTCCAAGGAGTAAGACC-3', reverse: 5'-AGGGGTCTACATGGCAACTG-3'. The relative expression of *ITPKA* was normalized to *GAPDH*, and calculated with $2^{-\Delta\Delta C_t}$ method.

2.4 | Immunohistochemistry analysis (IHC)

IHC analysis was performed to analyze ITPKA protein in BC patients. BC tissues and adjacent noncancerous tissues were paraffin-embedded and sliced into 4 μm sections. Firstly, all sections were deparaffinized using xylene. Then the sections were dehydrated with graded ethanol. The activity of endogenous peroxidase was inhibited with 3% hydrogen peroxide, and the activity of antigens was recovered through applying citrate buffer (pH 6.1). Then, the tissue sections were incubated with anti-ITPKA antibody (Abcam, ab251867, 1/2500) for one night at 4°C. Subsequently, the sections were incubated with the second antibody for 30 min at 4°C. Lastly, all sections were treated with streptavidin-horseradish peroxidase complex. The intensity of staining and the percentage of positively stained cells were graded by two experienced observers who had no information about these tissues. The intensity of staining was graded as: 0, no staining; 1, weak staining; and 2, moderate staining. The percentage of positively stained cells was defined as: 0, 0%; 1, <10%; 2, 10%–50%; and 3, >50%. Therefore, final score for *ITPKA* expression was graded as follows: 0–2, negative expression; and 3–6, positive expression.

2.5 | Statistical analysis

Data calculations were completed using SPSS 21.0 software. Continuous data in this study were expressed as

mean \pm SD, and their comparisons between two groups were performed using Student's *t* test. The associations of *ITPKA* expression with BC patients' clinicopathological features were analyzed via Chi-square test. To evaluate prognostic value of *ITPKA* expression, Kaplan–Meier survival curves and Cox regression analysis were adopted. *p* value less than .05 represented statistically significant threshold.

3 | RESULTS

3.1 | Expression of *ITPKA* in BC tissues

In the present study, the expression of *ITPKA* was examined with the method of qRT-PCR and IHC analysis in 132 BC tissues and adjacent noncancerous tissues. The results of qRT-PCR showed upregulated expression of *ITPKA* mRNA in BC samples compared with noncancerous samples ($p < .05$, Figure 1a). In accordance with this trend, IHC analysis showed that the expression score of *ITPKA* was significantly higher in BC tissues than in matched noncancerous tissue samples ($p < .05$, Figure 1b).

3.2 | Association of *ITPKA* expression with clinicopathological features of BC patients

Chi-square test was adopted to estimate the association of *ITPKA* expression with clinicopathological profiles in BC. From the results detailed in Table 1, we found that the expression of *ITPKA* was significantly correlated with lymph node metastasis ($p = .021$) and TNM stage ($p = .009$). Nonetheless, no relationship was found between *ITPKA* expression and patients' age, tumor size, expression of ER, PR or HER-2 (all $p > .05$).

3.3 | Prognostic value of *ITPKA* expression in patients with BC

Prognostic value of *ITPKA* was explored with Kaplan–Meier curve and Cox regression analysis. As displayed in Figure 2, overall survival was higher in patients with low expression of *ITPKA* than in those with high expression (log-rank test, $p < .05$). Cox regression analysis revealed that the expression of *ITPKA* was an independent prognostic factor, reaching a p value of .000, an HR of 4.239 and a 95%CI between 2.221 and 8.093 (Table 2).

4 | DISCUSSION

BC is a most common malignancy among women around the world (Buckley et al., 2015). The morbidity of BC is higher in developed countries than in developing regions, and varied from 27 per 100,000 females in Middle Africa to 96 per 100,000 in Western Europe (DeSantis et al., 2016; Siegel et al., 2013). So far, there are various therapeutic methods for BC in clinic, such as surgical operation, radiotherapy, and chemotherapy, but the patients' overall survival remains dismal (Fan et al., 2015). Novel and accurate biomarkers are in urgent need for BC diagnosis and surveillance. In recent years, a variety of biomarkers have been proposed for BC. For instance, Fu et al. demonstrated that decreased *SOX17* expression was correlated with poor prognosis of BC (Fu et al., 2015). MicroRNA-106b has been proven to be involved in the recurrence of BC, which might be an independent prognostic factor for the disease (Zheng et al., 2015). Katarzyna

and colleagues reported that thyroid hormone receptor α (*THRa*) might be an efficient prognostic biomarker in BC (Jerzak et al., 2015). In the present study, we assessed prognostic value of *ITPKA* in patients with BC.

ITPKA is a crucial member in the regulation of calcium signaling (Schell, 2010). It is usually expressed in neurons in neocortex, cerebellum, and hippocampus, and accumulates in dendritic spines given its association with F-actin (Schell et al., 2001; Vanweyenberg et al., 1995). Evidence demonstrated that *ITPKA*-induced actin cross-linking and the activity of filamin C could lead to the formation of new lamellipodia and filopodia, which are prerequisite for tumor cell migration and metastasis (Windhorst et al., 2008, 2010, 2011). Oncogenic role of *ITPKA* has been confirmed in several human cancers. In acute myeloid leukemia, the up-regulation of *ITPKA* reportedly contributed to malignant progression of the disease (Sonnet et al., 2014). Li et al. have proven that the over-expression of *ITPKA* in hepatocellular carcinoma might predict poor prognosis for the patients (Li et al., 2015). In BC, *ITPKA* has also been confirmed as a diagnostic biomarker (Wang et al., 2016). However, whether *ITPKA* could be employed as a prognostic biomarker for BC remained poorly known.

In the present study, the expression of *ITPKA* was examined with qRT-PCR and IHC methods. Analysis results showed that *ITPKA* expression was significantly increased in BC tissues at both mRNA and protein levels. Our findings were in accordance with those in previous study (Li et al., 2015). The relationship between *ITPKA* expression and clinicopathological profiles of BC patients was also investigated in the current study. Chi-square test showed that the expression of *ITPKA* was correlated with lymph node metastasis and TNM stage of BC patients. These results suggested that the up-regulation of *ITPKA* might contribute to malignant development of BC.

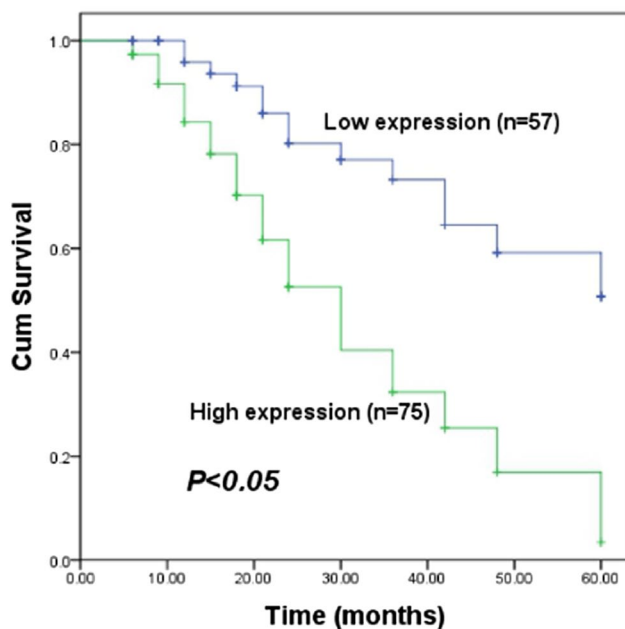


FIGURE 2 Kaplan–Meier survival curves based on the expression of *ITPKA* in BC

TABLE 2 Multivariate Cox regression analysis for *ITPKA* and clinical features in BC patients

Variables	Multivariate analysis		
	HR	95%CI	p value
<i>ITPKA</i> ^a	4.239	2.221–8.093	.000
Age	1.609	0.933–2.776	.087
Tumor size	1.359	0.785–2.352	.274
Lymph node metastasis	0.755	0.419–1.361	.350
PR expression	0.959	0.546–1.683	.884
ER expression	0.820	0.470–1.431	.484
HER-2 expression	0.607	0.352–1.048	.073
TNM stage	1.360	0.785–2.358	.273

Abbreviations: CI, confidence interval; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; HR, hazard ratio; PR, progesterone receptor.
^a*ITPKA* accession number: BC026331.1.

To evaluate prognostic value of *ITPKA* in BC, Kaplan–Meier survival and Cox regression analysis were employed. From the survival curves, we found that patients with low expression of *ITPKA* were more likely to enjoy longer survival time than those with high expression. Cox analysis demonstrated that the upregulated expression of *ITPKA* was independently correlated with dismal prognostic of BC. *ITPKA* might be a potential biomarker for prognosis evaluation in BC.

In summary, the expression of *ITPKA* was elevated in BC, which may be employed as a prognostic biomarker for patients with BC. Despite those encouraging findings, molecular mechanisms of *ITPKA* functioning in BC need to be further explored.

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None.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

All authors contributed to data analysis, drafting and revising the article. All the authors gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study could be obtained from the authors upon reasonable requirements.

ORCID

Hongying Pi  <https://orcid.org/0000-0003-1437-9368>

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