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ORIGINAL RESEARCH

Clinical Significance of ZNF711 in Human Breast Cancer

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Purpose: To investigate the clinicopathologic and prognostic significance of the zinc-finger protein 711 (ZNF711) in breast cancer (BCa).

Materials and Methods: The relevance of ZNF711 in BCa was analyzed using bioinformatics. The expression of ZNF711 was detected by immunohistochemistry in paraffin blocks of BCa. To evaluate its clinical significance, the correlation between the expression of ZNF711 and BCa clinical indicators, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2), was analyzed. Finally, the Kaplan–Meier method was applied to explore the prognostic value of ZNF711.

Results: ZNF711 expression was decreased in BCa and was negatively correlated with ER expression ($P < 0.05$) and positively correlated with HER-2 expression ($P < 0.01$), but there was no significant correlation between ZNF711 and PR expression. ZNF711 expression was not correlated with age, tumor diameter, or lymph node metastasis; however, ZNF711 expression was correlated with staging in BCa. Survival analysis results showed that the ZNF711-positive group patients had a poorer prognosis compared with the ZNF711-negative group.

Conclusion: The expression of ZNF711 was deceased in BCa and closely related to ER and HER-2 expression. Therefore, ZNF711 could not only serve as a predictor of BCa with poor prognosis but also as a potential biomarker for targeted therapy.

Keywords: breast cancer, zinc-finger protein 711, ER, HER-2

Introduction

Breast cancer (BCa) is the most common malignant tumor in women, accounting for 24.2% of female tumors worldwide, with a mortality rate of up to 15.0%.[1] The incidence rate of BCa is gradually increasing, especially in young patients.[2,3] The occurrence and development of BCa is a complex biological process involving multiple genes and proteins. Therefore, it is particularly important to identify new biomarkers and therapeutic targets for BCa.

Zinc-finger proteins are transcription factors with a "fingerlike" domain that are widely involved in many biological processes, such as cell differentiation, proliferation, and apoptosis in eukaryotes. It has been shown that zinc-finger proteins could also act as recruiters of chromatin modifiers, as co-factors, or as structural proteins involved in cell migration and invasion. Zinc-finger proteins are correlated with tumorigenesis and the development of multiple types of human cancers and may be useful as prognostic factors.[4–9]

ZNF711 is a newly discovered zinc-finger protein involved in the development of neurons. Recent studies have shown that ZNF711 is expressed in BCa cell lines,

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submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/OTT.S251702

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but its function and regulatory mechanisms are unclear.[8] In this study, the relevance of ZNF711 expression in breast tumors was analyzed using the UALCAN and kmplot databases, and the expression of ZNF711 in BCa tissue was assessed by immunohistochemical staining. Moreover, we explored the relationship between ZNF711 and clinical pathological factors in BCa.

Materials and Methods

Bioinformatics Analysis

The online database UALCAN (ualcan.path.uab.edu/) was used to obtain the differential expression levels of ZNF711 in BCa and normal breast tissues. The prognostic value of the expression of ZNF711 in BCa was evaluated using Kaplan–Meier survival analysis (kmplot.com/). The interconnection of ZNF711 with other regulatory genes was also explored using the STRING database (https://string-db.org/).

Patients and Tissues Samples

This study was approved by the Liaoning Cancer Hospital and Institute Ethics Review Board (#201601415). Paraffin-embedded specimens from breast surgeries were collected and screened from January 2001 to August 2002 at the Liaoning Cancer Hospital. None of these patients had previously been treated with chemotherapy or radiation therapy. After surgery, all patients received four to six cycles of chemotherapy and HER-2-positive patients received additional treatment with trastuzumab. Seventy-six breast cancer samples with histological types of invasive ductal carcinoma (IDH, 66 cases) and invasive lobular carcinoma (ILH, 10 cases) were included in this study; among them, luminal A (31 cases), luminal B (16 cases), HER-2-positive (17 cases), and basal-like (12 cases) according to the 12th St. Gallen International Breast Cancer Conference (2011).[10] These biological subtypes were based on immunohistochemical staining and fluorescence in situ hybridization (FISH). Eighteen cases of normal breast tissues were also collected. The clinical characteristics of the study participants were as follows: all patients were female, 33–79 years old, with an average age of 49 years. The maximum tumor diameter was 0.5–7.0 cm, with an average of 2.1 cm. There were 24 cases with lymph node metastasis and 23 cases were stage I, 50 cases were stage II, and 3 cases were stage III. Follow-up was performed for 150 months in all patients.

Main Reagents

Anti-human ZNF711 rabbit polyclonal antibody was purchased from Abcam (ab254776, 1:400, positive control: human cerebral cortex, cerebellum, and testis tissue, negative control: human liver tissue). Anti-HER-2 rabbit monoclonal antibody, anti-progesterone receptor (PR) rabbit monoclonal antibody, and anti-estrogen receptor (ER) rabbit monoclonal antibody were purchased from Roche Biotechnology Co., Ltd. (Basel, Switzerland). The secondary antibody and supporting staining reagents were purchased from Fuzhou Maixin Biotechnology Co., Ltd. (Fuzhou, China).

Immunohistochemical Staining

Paraffin sections of BCa tissues were baked for 2 h in a 60°C oven, and the slides were placed on a fully automated immunohistochemistry slide frame (Roche Bench Mark GX). The following conditions were used: dewaxing for 15 min, 0.01 mol/L sodium citrate antigen with heat treatment for 30 min, antibody incubation for 28 min, secondary antibody incubation for 8 min, DAB (diaminobenzidine) reaction for 8 min, hematoxylin staining for 12 min, and dye acceleration for 4 min. After the staining was completed, the sealed slides were dried for observation.

FISH Testing

Immunohistochemistry HER-2 (2+) cases were retested using FISH. The FISH analysis was performed on 3- to 5-lm-thick paraffin sections of tumor tissues using Paraffin Pretreatment Reagent Kit□and PathVysion HER-2 DNA Probe Kit (Gene Tech, Shanghai). Then, detecting the amplification of HER-2 gene followed the manufacturer's instructions. FISH results were expressed as the ratio between the number of copies of the HER2 gene and the number of copies of chromosome 17 within the nucleus counted in at least 20 cancer cells. The definition of FISH positivity was HER2: chromosome 17 ratio of ≥2.0 (Supplementary Figure 1).

Criteria for Interpretation of Results

In order to ensure the objectivity of the results, two pathologists blinded to the clinical data semi-quantitatively scored the slides by evaluating the staining intensity and percentage of stained cells. The staining intensity was scored on a scale of 1–3 (1, weak; 2, intermediate; 3, strong). The percentage of cells stained was graded on a scale of 1–4 (1, 1–25%; 2, 26–50%; 3, 51–75%; 4,

76–100%). The extent of staining was defined by H-score, the staining intensity score multiplied by the percentage of positive cells. For the interpretation of ZNF711 expression, a total score from 0 to 3 points indicated a negative result, and a score greater than or equal to 4 points indicated a positive result. The interpretation criteria for ER, PR, and HER-2 followed the clinically accepted guidelines of ASCO/CAP breast cancer hormone receptor IHC and the breast cancer HER-2 Detection Guide (2014 Edition).

Statistical Analysis

Data were analyzed using SPSS23.0. $P < 0.05$ was considered statistically significant. The χ^2 test was used to count the data. Spearman correlation analysis was used for hierarchical correlation analysis. The Kaplan–Meier method was used for survival analysis. The Log rank test was used to compare survival rates between the groups.

Results

Expression of ZNF711 in Normal Breast Tissue and BCa

The expression of ZNF711 protein in breast tissue is located in the cell nuclei (proteinatlas.org/). Bioinformatic analysis of 1097 patient samples from the TCGA database via UALCAN indicated that the expression of ZNF711 was decreased in BCa (Figure 1). Immunohistochemical staining demonstrated ZNF711 expression in normal tissues was decreased in BCa (mean score: 8.7 vs. 5.9, $P < 0.01$) (Figure 2). The negative rate of ZNF711 protein expression in BCa was significantly higher than that in normal tissues (60.5% vs. 0%, $P < 0.01$). However, 26.3% (20/76) of breast cancers had an immunohistochemical score of 12 for ZNF711 expression, which is higher than that in normal tissues (5.5%, $P < 0.01$). (Figures 2 and 3)

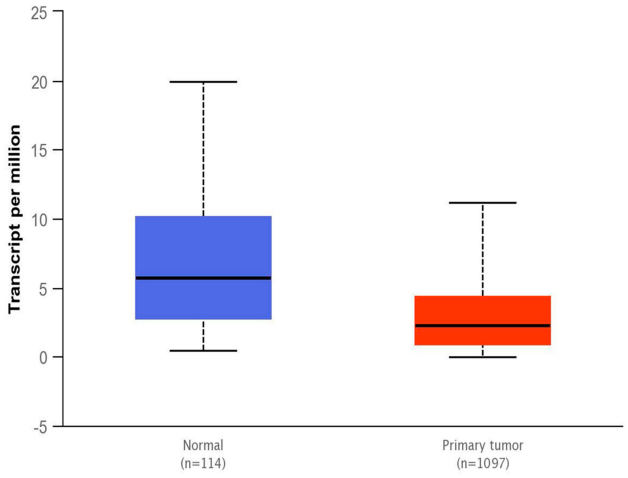


Figure 1 Expression of ZNF711 mRNA in normal breast tissues (normal) and BCa (primary tumor) based on TCGA database.

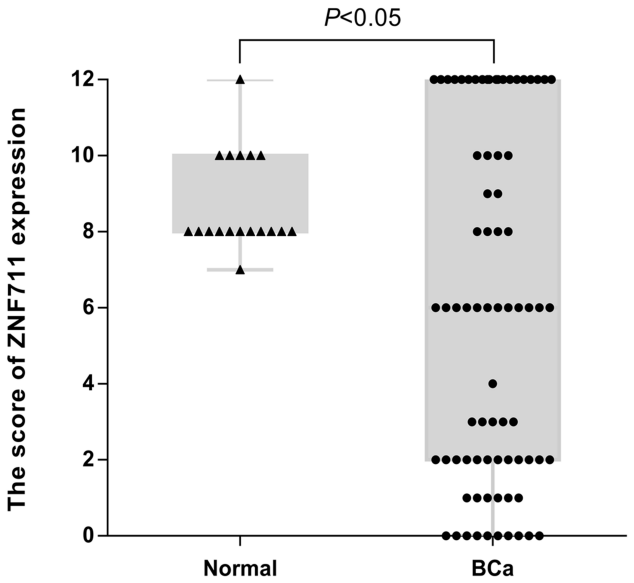


Figure 2 ZNF711 protein expression in normal breast tissues (normal) and BCa. *P*-values were obtained from Pearson chi-squared tests. The expression level of ZnF711 in BCa was lower than in normal tissues ($P < 0.05$).

Correlation Between ZNF711 Expression and Clinical Pathological Features in BCa

The expression of ZNF711 was not related to age, tumor diameter, lymph node metastasis, or histological type. However, its level was elevated in advanced breast cancer, as shown in Table 1. ZNF711 expression differed among the different molecular subtypes of BCa. Compared with luminal A type (4/31,13%) and basal-like breast cancer (3/12, 25%), ZNF711 expression was particularly high in luminal B type (9/16, 56%) and HER-2-positive breast cancer (14/17, 82%). ZNF711 expression was significantly higher in HER-2 positive breast cancer tissues ($P<0.01$).

Correlation Between ZNF711 Expression and HER-2, ER, and PR Expression in BCa

To further investigate why ZNF711 is expressed differently in different molecular subtypes of BCa and to explore the correlation with other biological markers of BCa, the correlation between ZNF711 expression and that of ER, PR, and HER-2 was determined in 76 breast cancer cases. Our results showed that ZNF711 was highly expressed in HER-2-positive BCa cells; however, ZNF711 expression was lower in ER-positive cancer tissues (Figures 4 and 5). The

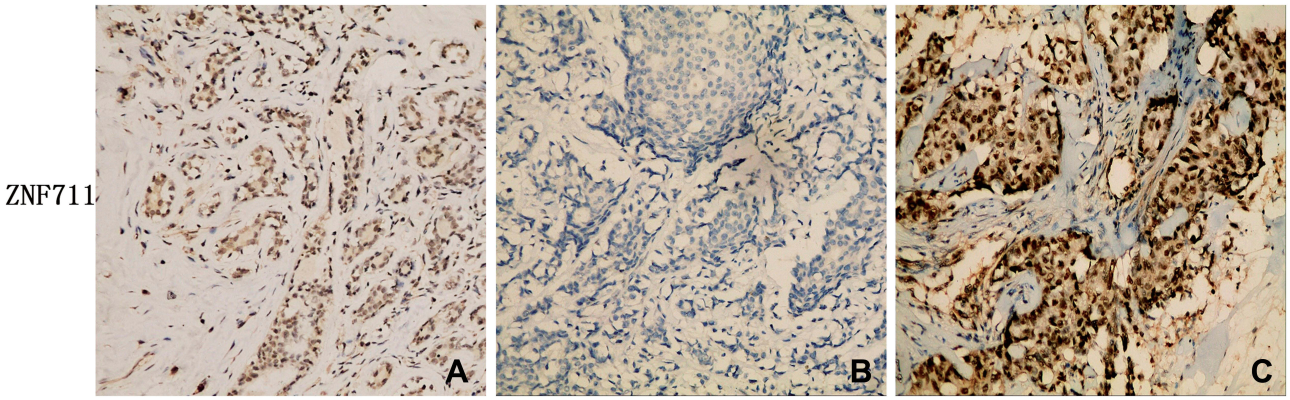


Figure 3 (**A**–**C**) ZNF711 expression and localization, as assessed by immunohistochemical staining, in normal breast tissues and BCa. ZNF711 was resided in cell nucleus, positive staining was light brown, in normal breast tissues (**A**). Staining intensity was negative or lower than normal in 60.5% of breast cancers (**B**), while it was dark brown in 26.3% of breast cancers (**C**) that is higher than normal.

correlation analyses are summarized in Table 2. In BCa, ZNF711 expression was positively correlated with HER-2 expression and negatively correlated with ER expression. There was no significant correlation between the expression of ZNF711 and PR ($P > 0.05$).

Prognostic Significance of ZNF711 in BCa

A total of 76 patients completed the follow-up period, and the mean survival time was 125.04 months in the ZNF711-negative group and 111.87 months in the ZNF711-positive group. Using the Kaplan–Meier method and the Log rank

Table 1 Correlation Between ZNF711 Expression and Clinical Pathological Features in Patients with BCa

Clinical and Pathological Features	ZNF711		Total Cases	χ^2	*P*
	Positive (%)	Negative (%)			
Age (Years)				0.464	0.496
≤54	20 (37%)	34 (63%)	54		
>54	10 (45%)	12 (55%)	22		
Tumor size (cm)				0.227	0.633
<2	7 (35%)	13 (70%)	20		
≥2	23 (41%)	33 (59%)	56		
Clinical stage				4.342	0.037
I	5 (22%)	18 (78%)	23		
II–III	25 (47%)	28 (53%)	53		
Lymph node metastasis				0.188	0.644
Negative	21 (41%)	30 (59%)	51		
Positive	9 (36%)	16 (64%)	25		
Histological type				0.147	0.701
IDC	25 (38%)	41 (62%)	66		
ILC	5 (50%)	5 (50%)	10		
Molecular subtype				26.853	0.000
Luminal A	4 (13%)	27 (87%)	31		
Luminal B	9 (56%)	7 (44%)	16		
HER2-positive	14 (82%)	3 (18%)	17		
Basal-like	3 (25%)	9 (75%)	12		

Note: χ^2, P-value obtained from Pearson chi-squared test.
Abbreviations: IDC, invasive ductal carcinoma, ILC, invasive lobular carcinoma.

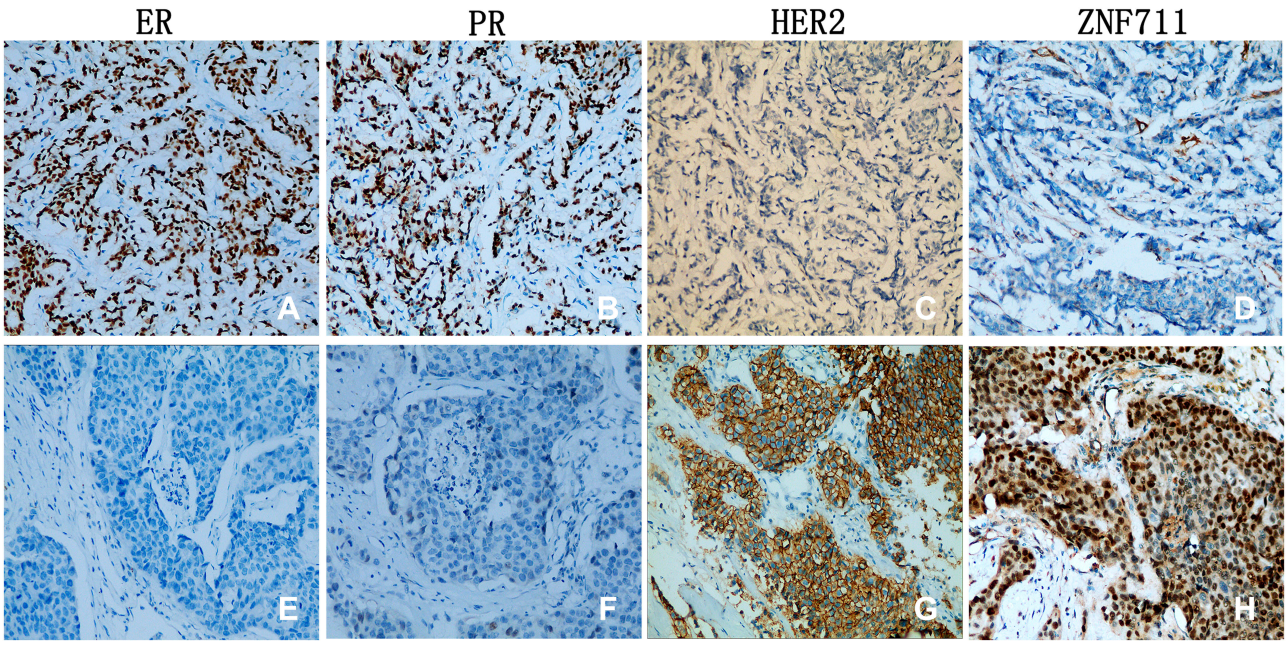


Figure 4 (**A–H**) The expression and localization of ER, PR, ZNF711 and HER-2, as assessed by immunostaining in BCa. ZNF711 was negative (**D**) in the BCa sample with ER^+(**A**), PR^+(**B**) and $HER\text{-}2^-$ (**C**) and ZNF711 was positive (**H**) in the BCa sample with ER^- (**E**), PR^-(**F**) and $HER\text{-}2^+$ (**G**).

test, the results indicated that high ZNF711 expression in BCa was significantly associated with poorer overall survival (Figure 6, $P < 0.05$). Multivariate Cox regression analysis was used to examine the relationship between survival time and clinical factors, including ZNF711 expression, which showed that high expression of ZNF711 (HR = 8.798, 95% CI: 2.070–37.224) was an independent prognostic factor for overall survival (Table 3). The KM plotter database also suggested that an increase in ZNF711 expression in BCa positively correlated with poor prognosis (Figure 7).

Interconnection of ZNF711 with Other Regulatory Genes

To explore the regulatory mechanism of ZNF in breast cancer, we further explored the interconnection of ZNF711 with other regulatory genes using the STRING database. We found that ZNF711 may directly bind with testis expressed sequence 13B (TEX13B), zinc finger CCCH-type containing 14 (ZC3H14), premature ovarian failure 1B (POF1B), magnesium transporter 1 (MAGT1), tripartite motif-containing 28 (TRIM28), and other genes

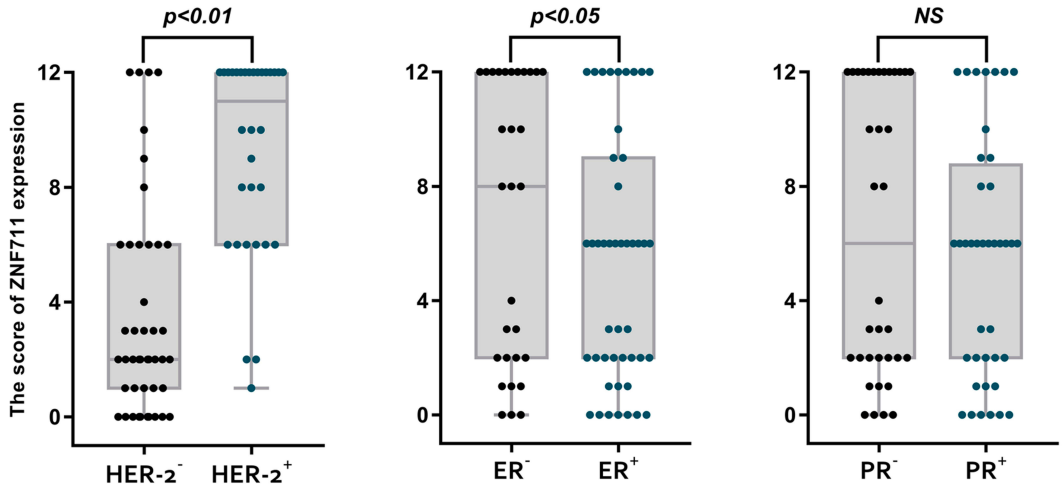


Figure 5 Correlation of ZNF711 expression with HER-2, ER, and PR in BCa. The expression of ZNF711 increased in $HER\text{-}2^+$ ($P < 0.01$). In contrast, the expression of ZNF711 decreased in ER^+. ($P < 0.05$).

to play an important role in regulating the progression of breast cancer (Supplementary Figure 2). However, the exact mechanisms of action need to be explored in the future.

Discussion

In 1982, Bogenhagen et al first discovered that the zinc-finger protein transcription factor IIIA (TFIIIA) is involved in the regulation of the 5S RNA gene in *Xenopus oocytes*, since then the regulatory roles of zinc-finger proteins have been studied in various taxa.[11–15] Zinc-finger proteins (ZNFs) are one of the most-abundant groups of proteins and are able to interact with nucleic acids and poly-ADP-ribose (PAR), as well as other proteins. ZNFs are implicated in transcriptional regulation, ubiquitin-mediated protein degradation, signal transduction, actin targeting, DNA repair, cell migration, and other biological processes.[8] Previous studies have demonstrated that zinc-finger protein 148 (ZNF148) and zinc-finger E-box-binding protein 1 (ZEB1) are involved in the development and epithelial-to-mesenchymal transition (EMT) of breast cancer.[16–20]

The ZNF711 gene is located at Xq21.1–q21.2 and encodes a zinc-finger protein with unknown function. The protein contains a potential domain at the amino terminal that may be involved in transcriptional activation, together with 12 Zn-C2H2 domains that are involved in sequence-specific DNA binding. The ZNF711 gene is predominantly expressed in the brain and testis of humans and is an important transcription factor in the development of X chromosome-related intelligence.[21] ZNF711 and zinc-finger protein X-linked (ZFX) are known to bind to gene promoter regions in the breast cancer cell line MCF7 and participate in transcriptional regulation.[9] However, the specific function and mechanism of ZNF711 in breast cancer cells remain unclear. In this study, the association between ZNF711 expression and clinical characteristics was analyzed in breast cancer patients.

Bioinformatic analysis and immunohistochemical staining were performed to detect the expression of ZNF711 in human normal and cancerous breast tissues. ZNF711 is expressed in normal tissues and decreased in BCa (Figures 1 and 2). ZNF711 expression was reduced in most breast cancers, but was still strongly expressed in 26.3% of breast cancers, which is higher than in normal tissues (Figures 2 and 3). Thus, a paradox emerges: how can ZNF711 in BCa have a polarized mode of expression?

To explore the polarization of ZNF711 expression in BCa, the correlation between ZNF711 expression and clinical pathological features was investigated. The expression of ZNF711 did not correlate with age, tumor size, lymph node metastasis, and histological type (Table 1). ZNF711 expression was significantly higher in advanced breast cancer (stage II–III) than in the early stage (stage I), suggesting that ZNF711 expression is associated with poor prognosis. The expression of ZNF711 was different among different molecular subtypes of BCa, and was significantly higher in HER-2-positive breast cancer tissues and lower in ER-positive cancer tissues (Figures 4 and 5).

The correlation between ZNF711 expression and HER-2, ER, and PR was analyzed in BCa, where expression was positively correlated with HER-2 expression and negatively correlated with ER expression (Table 2). There

Table 2 Correlation of ZNF711 Expression with HER2, ER, and PR in BCa

	ZNF711		Total Case	χ^2	*r*	*P*
	Positive (%)	Negative (%)				
ER				6.132	−0.284	0.013
Negative	17 (57%)	13 (43%)	30			
Positive	13 (28%)	33 (72%)	46			
PR				3.172	−0.204	0.075
Negative	18 (50%)	18 (50%)	36			
Positive	12 (30%)	28 (70%)	40			
HER-2				24.288	0.565	0.000
Negative	7 (16%)	37 (84%)	44			
Positive	23 (72%)	9 (28%)	32			

Notes: χ^2, P-value was obtained from the Pearson chi-squared test. *r*-Value was obtained from the Spearman rank correlation test.

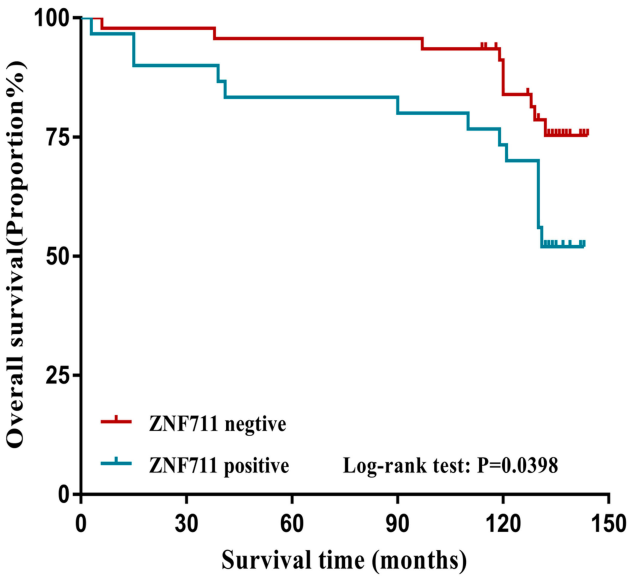


Figure 6 Survival curves for ZNF711-positive and -negative patients with BCa.

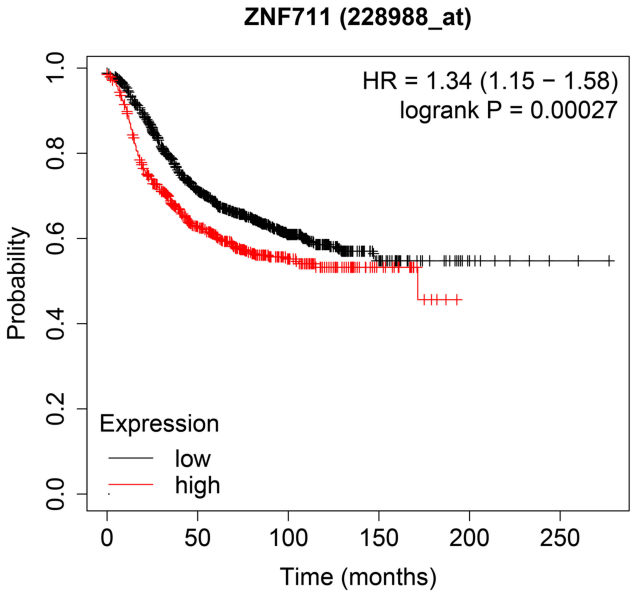


Figure 7 Survival curves for ZNF711-positive and -negative patients based on Kmplot database.

was no significant correlation between the expression of ZNF711 and PR. Therefore, we hypothesize that the expression of HER-2 and ER may play an important role in ZNF711 gene transcription regulation in BCa.

Although the expression of ZNF711 was decreased in BCa, the survival analysis showed that the ZNF711-positive group patients had a poorer prognosis and a lower survival rate compared with the ZNF711-negative group ($P < 0.05$). Gene amplification and overexpression of HER-2 have been found in many human cancers, which correlate with the genesis and progress of tumors as well as aggressive biological behaviors. The majority of patients in the ZNF711-positive group (76.7%) were also HER-2 positive (Table 1). Therefore, we believe that this may be the reason for the poor prognosis in the ZNF711-positive group.

Currently, only 20% to 40% of patients with advanced hormone receptor-positive breast cancer respond to first-line endocrine therapy, and about 50% of these patients exhibit recurrence and metastasis due to resistance to endocrine therapy after approximately 14 months.[22] Laurentiis et al[23] found that endocrine therapy is less effective in patients with HER-2-positive breast cancer, but Ellis et al[24] believed that HER-2-positive is not always a marker of endocrine resistance. The specific mechanism of action is still unclear. In this study, the expression of ZNF711 was found to be closely related to the expression of HER-2 and ER; however, whether it participates in the regulatory mechanism between them needs to be studied further.

Table 3 Multivariate Analysis for Overall Survival by Cox Regression Model

Variable	HR	95% CI	P
ZNF711 Expression	8.798	2.070–37.224	0.003
Clinical stage	0.69	0.279–1.704	0.421
Molecular subtype			
Luminal B/Luminal A	1.364	0.0461–4.038	0.575
HER2-positive/Luminal A	2.131	0.523–8.688	0.291
Basal-like/Luminal A	5.332	1.195–23.792	0.028

In summary, the expression of ZNF711 is closely related to the development and prognosis of BCa, and the expression of ZNF711 is significantly correlated with the expression of ER or HER-2. Therefore, ZNF711 may be a novel biomarker for predicting poor prognosis and may serve as a potential therapeutic target for BCa. Furthermore, we also investigated potential ZNF711-binding proteins, which may help to explore the regulation mechanism of ZNF711 in the development of breast cancer.

Abbreviations

BCa, breast cancer; ZNF711, zinc-finger protein 711; ER, estrogen receptor; PR, progesterone receptor; HER-2, erb-b2 receptor tyrosine kinase 2; ZNFs, Zinc-finger proteins; ZFX, zinc-finger protein X-linked; FISH, fluorescence in situ hybridization; IDH, invasive ductal carcinoma; ILH,

invasive lobular carcinoma; DAB, diaminobenzidine; TEX13B, testis expressed sequence 13B; ZC3H14, zinc finger CCCH-type containing 14; POF1B, premature ovarian failure 1B; MAGT1, magnesium transporter 1; TRIM28, tripartite motif-containing 28; TFIIIA, transcription factor IIIA; ZNF148, zinc-finger protein 148; ZEB1, zinc-finger E-box-binding protein 1; EMT, epithelial-to-mesenchymal transition.

Highlights

ZNF711 was expressed at lower levels in breast cancer. ZNF711 was highly expressed in breast cancer with high HER-2 expression. In breast cancer, ZNF711 expression was negatively correlated with ER expression. The patients in the ZNF711-positive group had a poor prognosis.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

All aspects of this study were approved by the ethics committee of Liaoning Cancer Hospital under protocol 20,170,304 (project approval date 03/16/2017). Ethical practices were followed throughout to cover patient data confidentiality and compliance with the Declaration of Helsinki.

Acknowledgments

The authors would like to thank Liqun Chen and Yue Zhang for their excellent technical support.

Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

The funding for this submission comes from the Natural Science Foundation of Liaoning Province, #201601415.

Disclosure

Dr Qiang Li reports grants from the Natural Science Foundation of Liaoning Province during the conduct of the study. The authors declare that they have no other competing interests.

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