

ORIGINAL RESEARCH

Correlation study of ultrasound signs of breast cancer with THRSP and ACACA protein expression

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Abstract

Background: This study aimed to investigate the correlation between ultrasound signs of breast cancer and the expression of thyroid hormone response protein Spot14 (THRSP) and Acetyl CoA carboxylases 1 (ACACA). **Methods:** A retrospective analysis was conducted on 150 patients with pathologically confirmed breast cancer who were admitted to our hospital between January 2022 and December 2023. Ultrasound signs of breast lesions were assessed, and the expression levels of THRSP and ACACA proteins in tumor and adjacent normal tissues were analyzed by immunohistochemistry. **Results:** The percentage of high THRSP and ACACA expression was significantly higher in tumor tissues compared to paracancerous tissues ($p < 0.05$). Patients with irregular mass morphology, diameter ≥ 2 cm, rich blood flow, and lymph node metastasis exhibited significantly higher THRSP and ACACA expressions than those with regular morphology, diameter < 2 cm, lack of blood flow, and no lymph node metastasis ($p < 0.05$). Expression of THRSP and ACACA protein was positively correlated with irregular tumor morphology, lesion diameter ≥ 2 cm, abundant vascularity, and lymph node metastasis ($p < 0.05$). Multivariate logistic regression analysis identified irregular mass morphology, lymph node metastasis, and clinical stage III as independent risk factors for high THRSP expression ($p < 0.05$), while irregular mass morphology, lymph node metastasis, mass diameter ≥ 2 cm, and clinical stage III were independent risk factors for high ACACA expression ($p < 0.05$). **Conclusions:** Ultrasound signs were significantly associated with THRSP and ACACA expressions in breast cancer tissues. These findings provide preliminary evidence supporting the potential of integrating imaging characteristics with molecular markers to enhance the diagnostic and prognostic evaluation of breast cancer.

Keywords

Breast cancer; Ultrasound signs; Thyroid hormone response protein Spot14; Acetyl CoA carboxylases 1

1. Introduction

Breast cancer ranks first among malignant tumors in Chinese women, accounting for approximately 15% of all female cancer deaths, with its incidence continuing to rise annually [1]. Early diagnosis and timely treatment are critical for improving patient survival outcomes [2]. In recent years, advances in ultrasound technology have enhanced its utility in the diagnosis, treatment planning, and prognostic assessment of breast cancer. Ultrasound imaging provides real-time, non-invasive visualization of tumor characteristics such as morphology, size, internal echoes, and blood flow, offering essential information for the initial clinical evaluation of breast lesions [3]. However, sole reliance on ultrasonography has limitations, particularly in accurately assessing the biological behavior of tumors.

With the rapid development of molecular biology in oncology, an increasing number of genes associated with breast can-

cer have been identified. Several studies have suggested that ultrasound signs may correlate with molecular subtypes and biological behaviors of breast cancer [4]. This raises the possibility that breast ultrasound, in addition to structural evaluation, may serve as a non-invasive approach for preliminary molecular diagnosis, facilitating more personalized treatment and prognosis assessment in clinical practice [5]. Among emerging molecular markers, thyroid hormone response protein Spot14 (THRSP) and Acetyl CoA carboxylases 1 (ACACA) have attracted attention due to their roles in lipid metabolism reprogramming during tumor progression. THRSP promotes tumor cell proliferation, invasion, and metastasis by activating signaling pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) [6]. Breast cancer cells exhibit increased lipogenesis to support rapid proliferation, ACACA—an enzyme involved in fatty acid biosynthesis—provides essential substrates for membrane construction and energy supply,

facilitating tumor development and progression [7]. While overexpression of THRSP and ACACA has been reported in several solid tumors, including hepatocellular carcinoma and colorectal carcinoma [5, 8]. However, their roles in breast cancer remain underexplored. Moreover, few studies have investigated the relationship between the expression of these two proteins and breast ultrasound features.

Given this gap, this study aims to investigate the association between breast cancer ultrasound signs and the expression of THRSP and ACACA. By integrating imaging features with molecular biomarker expression, this study seeks to deepen our understanding of tumor biology from a radiogenomic perspective and provide a more comprehensive reference for the early diagnosis, clinical assessment, and treatment of breast cancer.

2. Materials and methods

2.1 Patients

This retrospective study included 150 breast cancer patients treated at Xinjiang Medical University Affiliated Tumor Hospital between January 2022 and December 2023. Inclusion criteria: (1) All patients had pathologically confirmed breast cancer based on tissue specimens obtained by surgical excision or puncture biopsy; (2) None had received anti-tumor therapies such as chemotherapy, radiotherapy or endocrine therapy before surgery; (3) All patients provided written informed consent and voluntarily participated in this study. Exclusion criteria: (1) Patients with other malignant tumors; (2) Patients with severe comorbidities such as significant hepatic or renal dysfunction, or cardiopulmonary insufficiency, which could impair surgical tolerance or confound study outcomes; (3) Patients with mental illnesses who were unable to cooperate with examinations or follow instructions.

2.2 Ultrasonography

Breast ultrasonography was performed using an ultrasonic instrument (HDI3000, PHILIP, Best, Netherlands), with transducers operating at 5–12 MHz. Scanning began at the nipple

and areola, followed by a systematic inside-out and top-down examination of the entire breast. Observed parameters included lesion size, boundary characteristics, calcification, and blood flow. Ultrasound images were independently reviewed by 2 experienced chief physicians using a double-blind method (Table 1). In cases of disagreement, consensus was obtained through consultation to ensure objectivity and reliability of image interpretation.

2.3 Immunohistochemical analysis

Breast cancer tissues were paraffin-embedded, and 4 μ m-thick sections were prepared. Sections were baked, dewaxed, and rehydrated, followed by citric acid antigen repair solution (pH = 6.0) for 2 min. After rinsing with phosphate buffer solution (PBS), sections were incubated with 3% hydrogen peroxide at room temperature for 10 min. Subsequently, after PBS washes, sections were incubated at room temperature for 1 h with primary antibodies: rabbit anti-human THRSP polyclonal antibody (1:500 dilution, #MBS7044116, MyBioSource, San Diego, CA, USA) and mouse anti-human ACACA polyclonal antibody (1:2000 dilution, #MBS620207, MyBioSource, San Diego, CA, USA). Ready-to-use MaxVision detection reagent was then added and incubated at room temperature for 15 min. 3,3'-Diaminobenzidine was used for chromogenic development, and hematoxylin was used for counterstaining. Sections were rinsed with PBS, dehydrated with gradient ethanol, and fixed with xylene clear, neutral gum. Immunostaining was evaluated using Image-Pro Plus 7.0 computer image analysis software (Media Cybernetics, Rockville, MD, USA). Yellowish, tan, or brownish staining in the nucleus or cytoplasm was considered positive. The results were determined by two experienced pathologists. Two experienced pathologists independently assessed the sections and scored them based on both staining intensity and the percentage of positive cells: (1) $<5\%$ = 0, 5% to 25% = 1, 25% to 50% = 2, 50% to 75% = 3, and $>75\%$ = 4; (2) staining intensity: no staining = 0, yellow or light yellow = 1, brownish yellow = 2, and tan = 3. Staining index (SI) = proportion of positive cells $\times$ staining intensity, SI

TABLE 1. Specific ultrasound signs of breast cancer.

Ultrasound manifestation	Specific description
Mass morphology	Typically irregular in shape with spiny or crab-like edges, and the boundary with the surrounding tissues is unclear.
Diameter of the mass	Lesion size varied from a few millimeters to several centimeters. Early-stage breast cancers tend to be smaller, increasing in size with disease progression.
Mass boundary	The boundary is fuzzy and there is no obvious envelope. The invasive growth of cancer cells makes there is no clear boundary between the mass and the surrounding normal tissue, which is one of the important differences between breast cancer and benign mass.
Blood flow situation	Assessed using the Adler semi quantitative scoring system. Grade 0: no detectable blood flow; Grade 1: a small amount of blood flow, 1–2 punctate or short rod-shaped blood vessels can be seen; Grade 2: moderate blood flow, 3–4 punctate vessels or 1 long vessel can be seen; Grade 3: abundant blood flow, visible ≥ 5 punctate vessels, or 2 or more longer vessels. Grade 3 was defined as “abundant blood supply”.
Axillary lymph nodes	Enlarged lymph nodes may be present, characterized by abnormal lymph node morphology, thickening of the cortex, disappearance of the medulla, and increased blood flow signals—suggestive of lymph node metastasis.

>3 points was defined as high expression, $SI \leq 3$ was recorded as low expression.

2.4 Statistical analysis

Data analysis was performed using SPSS 26.0 (IBM, Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ standard deviation, and comparisons between two groups were conducted using independent sample *t*-tests. Categorical variables were expressed as the number of cases and rate; comparisons were performed using the chi-square (χ^2). Spearman correlation analysis was used to examine the correlation between ultrasound signs of breast cancer and THRSP and ACACA protein expression. Multivariate logistic regression analysis was conducted to identify independent risk factors associated with high expression of THRSP and ACACA proteins in breast cancer tissues. A *p*-value of < 0.05 was considered statistically significant.

3. Results

3.1 Ultrasound characteristics of breast cancer patients

Among 150 breast cancer patients, ultrasound revealed irregular mass morphology in 98 cases, tumor diameters ≥ 2 cm in 87 cases, rich blood flow signal in 89 cases, and lymph node metastasis in 68 cases. Representative sonographic images of typical cases are presented in Fig. 1.

3.2 Comparison of THRSP and ACACA protein expression in cancerous and paracancerous tissues

THRSP and ACACA protein expression in breast cancer tissues was predominantly localized in the cytoplasm, exhibiting a pale yellow to tan staining pattern (Fig. 2). The percentage of high THRSP and ACACA expression in tumor tissues was significantly higher than that in paracancerous tissues ($p < 0.05$, Table 2).

3.3 THRSP and ACACA protein expression in breast tissues of patients with different ultrasound signs

No statistically significant differences were observed in the high expression rates of THRSP and ACACA proteins in relation to tumor margin characteristics ($p > 0.05$). However, patients presenting with irregular mass morphology, tumor diameter ≥ 2 cm, rich blood-supplied blood flow, and lymph node metastasis exhibited significantly higher expression levels of both proteins compared to those with regular morphology, tumor diameter <2 cm, lack of blood-supplied blood flow, and no lymph node metastasis ($p < 0.05$, Table 3).

3.4 Correlation between ultrasound signs and THRSP and ACACA protein expression

Spearman’s correlation analysis demonstrated a significant positive correlation between high THRSP and ACACA protein expression and the presence of irregular mass morphology, diameter ≥ 2 cm, rich blood flow signals, and lymph node metastasis ($p < 0.05$, Table 4). No significant correlation was observed between margin burr and high expression of THRSP and ACACA protein ($p > 0.05$, Table 4).

3.5 Other factors that may affect THRSP and ACACA protein expression

Patients with clinical stage III breast cancer exhibited significantly higher THRSP and ACACA expression in tumor tissues compared to those with stage I–II ($p < 0.05$, Table 5).

3.6 Multivariate logistic regression analysis of THRSP and ACACA protein high expression

In the logistic regression analysis, THRSP protein expression was set as the dependent variable (high expression = 1, low expression = 0). The independent variables included mass morphology (irregular = 1, regular = 0), mass diameter (≥ 2 cm = 1, <2 cm = 0), blood flow (rich blood supply = 1, lack of blood supply = 0), lymph node metastasis (yes = 1, no = 0), and clinical staging (stage III = 1, stage I–II = 0) Multicollinearity

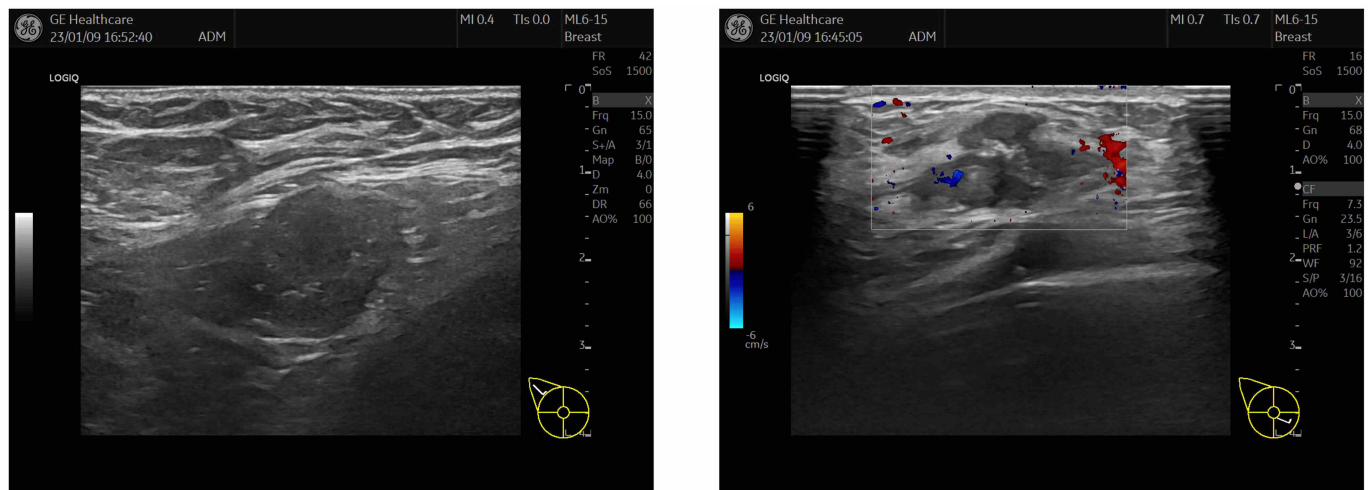


FIGURE 1. Ultrasound signs of breast cancer.

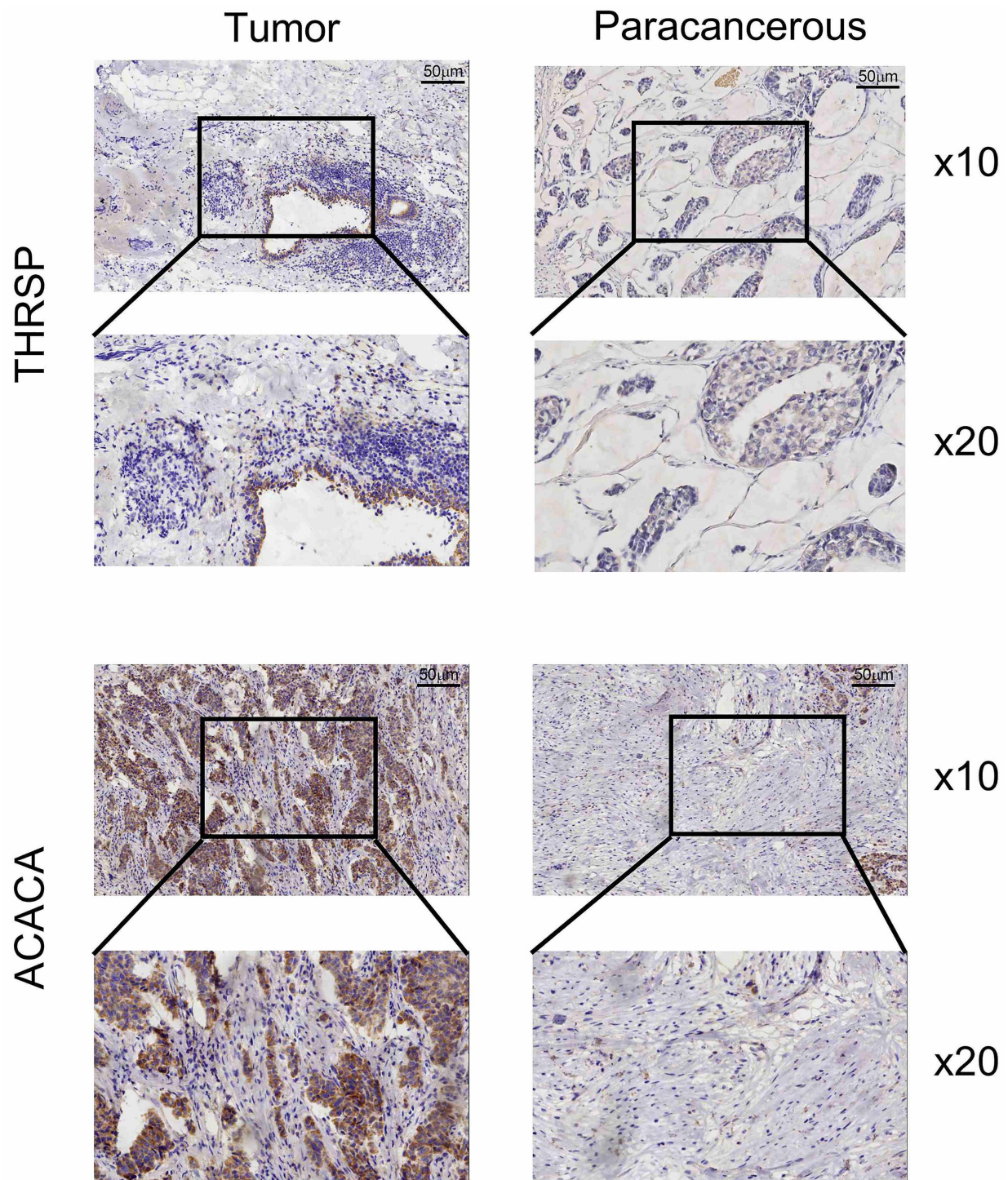


FIGURE 2. THRSP and ACACA protein expression in breast cancer and paracancerous tissues detected by immunohistochemical analysis. THRSP, thyroid hormone response protein Spot14; ACACA, Acetyl CoA carboxylases 1.

TABLE 2. Comparison of THRSP and ACACA protein expression in cancerous and paracancerous tissues.

Group	n	THRSP protein		ACACA protein	
		High expression	Low expression	High expression	Low expression
Tumor tissues	150	65 (43.33)	85 (56.67)	68 (45.33)	82 (54.67)
Paracancerous tissues	150	32 (21.33)	118 (78.67)	35 (23.33)	115 (76.67)
χ^2		16.591		16.101	
<i>p</i>		<0.001		<0.001	

THRSP, thyroid hormone response protein Spot14; ACACA, Acetyl CoA carboxylases 1.

TABLE 3. THRSP and ACACA protein expression in breast tissues of patients stratified by ultrasound signs.

Ultrasound Signs	n	THRSP protein			ACACA protein		
		High expression	χ^2	<i>p</i>	High expression	χ^2	<i>p</i>
Lump morphology							
Regular	52	15 (28.85)	6.803	0.009	10 (19.23)	21.882	<0.001
Irregular	98	50 (51.02)			58 (59.18)		
Diameter of the mass							
≥2 cm	87	45 (51.72)	5.939	0.015	54 (62.07)	23.411	<0.001
<2 cm	63	20 (31.75)			14 (22.22)		
Margin burr							
Yes	94	45 (47.87)	2.113	0.146	47 (50.00)	2.213	0.137
No	56	20 (35.71)			21 (37.50)		
Blood flow							
Rich blood supply	89	48 (53.93)	10.013	0.002	52 (58.43)	15.140	<0.001
Lack of blood supply	61	17 (27.87)			16 (26.23)		
Lymph node metastasis							
No	82	25 (30.49)	12.155	<0.001	28 (34.15)	9.134	0.003
Yes	68	40 (58.82)			40 (58.82)		

THRSP, thyroid hormone response protein Spot14; ACACA, Acetyl CoA carboxylases 1.

TABLE 4. Correlation between ultrasound signs and THRSP and ACACA protein expression.

Ultrasound Signs	THRSP high expression		ACACA high expression	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Irregular shape of the mass	0.213	0.009	0.382	<0.001
Diameter of the mass ≥2 cm	0.199	0.015	0.395	<0.001
Hairy edges	0.119	0.148	0.121	0.139
Rich blood supply and blood flow	0.258	0.001	0.318	<0.001
Lymph node metastasis	0.285	<0.001	0.247	0.002

THRSP, thyroid hormone response protein Spot14; ACACA, Acetyl CoA carboxylases 1.

TABLE 5. THRSP and ACACA protein expression in tumor tissue of breast cancer patients with different clinical parameters.

Factors	n	THRSP protein			ACACA protein		
		High expression	χ^2	<i>p</i>	High expression	χ^2	<i>p</i>
Age (yr)							
>50	63	25 (39.68)	0.590	0.443	28 (44.44)	0.035	0.852
≤50	87	40 (45.98)			40 (45.98)		
BMI							
≥24	25	11 (44.00)	0.005	0.941	10 (40.00)	0.344	0.557
<24	125	54 (43.20)			58 (46.40)		
Menopausal							
Yes	87	43 (49.43)	3.131	0.077	43 (49.43)	1.400	0.237
No	63	22 (34.92)			25 (39.68)		
Clinical Stage							
Stage I–II	89	27 (30.34)	15.054	<0.001	32 (35.96)	7.767	0.005
Stage III	61	38 (62.30)			36 (59.02)		

THRSP, thyroid hormone response protein Spot14; ACACA, Acetyl CoA carboxylases 1; BMI, body mass index.

was assessed using variance inflation factor (VIF), and all VIF of the above independent variables were <5 , indicating no significant multicollinearity among the independent variables. A forward stepwise logistic regression model was used for multivariate analysis. The results identified irregular mass morphology, lymph node metastasis, and clinical stage III as significant risk factors for high THRSP protein expression ($p < 0.05$, Table 6).

Similarly, ACACA protein expression was set as the dependent variable (high expression = 1, low expression = 0), with the same set of independent variables: mass morphology (irregular = 1, regular = 0), mass diameter (≥ 2 cm = 1, <2 cm = 0), blood flow situation (rich blood supply = 1, lack of blood supply = 0), lymph node metastasis (yes = 1, no = 0), and clinical staging (Stage III = 1, Stage I–II = 0). All VIF remained <5 , confirming the absence of multicollinearity. Multivariate analysis using the forward method revealed that irregular mass morphology, lymph node metastasis, mass diameter ≥ 2 cm, and clinical stage III were independent risk factors for high ACACA protein expression ($p < 0.05$, Table 7).

4. Discussion

Early clinical manifestations of breast cancer are often atypical. As a result, many patients miss the optimal window for intervention, posing a significant threat to women's health [9]. Currently, color Doppler ultrasound is mostly used in clinical settings, providing diagnostic insights through morphological features, margins, blood flow and other characteristics. In parallel, accumulating clinical evidence suggests that breast cancer progression is associated with aberrant abnormal expression of various proteins [10]. While correlations between ultrasound signs and several breast cancer markers such as estrogen-progesterin receptor, human epidermal growth factor receptor 2 (HER-2), and Kiel 67 (Ki-67) have been extensively studied [11, 12]. However, the correlation between THRSP and ACACA protein expression and ultrasound signs of breast cancer remains poorly understood.

Our findings demonstrate that THRSP and ACACA expression is significantly upregulated in breast cancer tissues,

suggesting their involvement in tumorigenesis and disease progression. THRSP, under normal physiological conditions, regulates intracellular lipid metabolism [13]. Its high expression in breast cancer tissues may disrupt metabolic homeostasis, favoring tumor cell growth and proliferation. Specifically, THRSP may enhance intracellular fatty acid synthesis and accumulation by upregulating lipid metabolism-related genes, supplying both energy and raw materials for biofilm synthesis for the rapid proliferation of tumor cells [14]. Further, THRSP may interact with intracellular signaling pathways, influencing key processes such as cell cycle progression and apoptosis, thus promoting tumor cell survival and proliferation [15]. Likewise, ACACA, a rate-limiting enzyme for fatty acid synthesis, is markedly upregulated in breast cancer. Its overexpression facilitates excessive lipid production, satisfying the increased metabolic demands of proliferating tumor cells and contributing to membrane remodeling, invasion, and metastasis [16].

This study further reveals a strong association between ultrasound signs of breast cancer and the high expression of THRSP and ACACA. During tumor progression, enhanced lipid metabolism leads to increased fatty acid synthesis, providing the material and energetic foundation for rapid cell proliferation and expansion, which may explain the observed increase in tumor size [17]. Irregularity tumor morphology on ultrasound often indicates disorganized and invasive growth pattern. Such irregularity is linked to reduced intercellular adhesion, enhanced motility, and aggressive invasion of surrounding tissues [18]. The high expression of THRSP and ACACA may drive these morphological changes by modulating key metabolic and signaling cascades, leading to irregular mass morphology [19]. In terms of tumor invasiveness and metastasis, the metabolic reprogramming induced by THRSP and ACACA overexpression may reshape the tumor microenvironment. Elevated cytokine and chemokine secretion can recruit tumor-associated macrophages, lymphocytes, and mesenchymal stromal cells, which together construct a pro-invasive niche [20]. Additionally, rich blood flow signals on ultrasound is consistent with active angiogenesis, which provides essential nutrients and oxygen, promoting further

TABLE 6. Multivariate logistic regression analysis of factors associated with high THRSP protein expression.

Factors	β	SE	Wald	OR	95% CI	p value
Irregular shape of the mass	1.038	0.408	6.461	2.824	1.268–6.289	0.011
Lymph node metastasis	1.344	0.382	12.372	3.834	1.813–8.107	<0.001
Clinical staging stage III	1.506	0.387	15.158	4.508	2.112–9.621	<0.001

SE, standard error; OR, Odds Ratio; CI, confidence interval.

TABLE 7. Multivariate logistic regression analysis of factors associated with high ACACA protein expression.

Factors	β	SE	Wald	OR	95% CI	p value
Irregular shape of the mass	1.769	0.471	14.134	5.867	2.332–14.757	<0.001
Lymph node metastasis	1.361	0.422	10.384	3.900	1.704–8.926	0.001
Lump diameter ≥ 2 cm	1.626	0.431	14.248	5.084	2.185–11.829	<0.001
Clinical stage III	0.990	0.416	5.663	2.691	1.191–6.083	0.017

SE, standard error; OR, Odds Ratio; CI, confidence interval.

tumor growth and dissemination.

Previous studies have primarily focused on the relationship between ultrasound signs of breast cancer and traditional tumor markers. In contrast, the present study innovatively incorporates THRSP and ACACA, two key proteins involved in lipid metabolism. Our findings demonstrate that ultrasound signs—irregular mass morphology, positive lymph node metastasis, and late clinical stage—are significantly associated with high THRSP expression. Similarly, ACACA expression showed consistent associations with several ultrasound signs. These results extend beyond the scope of traditional imaging-marker correlations, providing novel insights into the intrinsic connection between ultrasound signs and tumor metabolism. To further investigate the risk factors affecting the high expression of THRSP and ACACA, a multivariable logistic regression analysis was conducted. The results confirmed that multiple ultrasound manifestations independently predict high expression levels of these proteins. Tumor clinical staging reflects the extent of tumor invasion, lymph node involvement, and distant metastasis, thereby serving as a proxy for tumor progression and severity [21]. In the early stages of the tumor (stage I–II), the tumor's proliferative and invasive capacities are relatively limited, potentially corresponding to lower expression of THRSP and ACACA. However, as the tumor progresses, cancer cells may upregulate lipid metabolism by increasing THRSP and ACACA expression to fuel rapid proliferation, invasion, and metastasis. This metabolic adaptation likely contributes to the higher expression levels observed in stage III tumors. Ultrasound imaging offers several clinical advantages, including accessibility, non-invasiveness, and high reproducibility. If specific protein expression patterns—such as THRSP and ACACA—can be reliably inferred from ultrasound signs, this approach could significantly reduce diagnostic costs and risks of examination for patients.

Nevertheless, this study has several limitations. First, the relatively small sample size may affect the generalizability and representativeness of the findings. Future studies include larger, multicenter cohorts to validate these results. Second, although key risk factors for THRSP and ACACA expression were identified, breast cancer is a multifactorial disease influenced by complex interactions among genes, proteins, and environmental exposures. Future studies should incorporate these diverse variables to construct a more robust and comprehensive risk prediction model for breast cancer, ultimately supporting earlier detection and more personalized therapeutic strategies.

5. Conclusions

In conclusion, the high expression of THRSP and ACACA proteins in breast cancer tissues is closely correlated with specific ultrasound signs. These findings offer new theoretical insights and practical value for improving the diagnostic and prognostic assessment of breast cancer.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

HML, TL—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. HML, TL, WWL, SC, XS—supervised the data collection; analyzed the data; interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Xinjiang Medical University Affiliated Tumor Hospital (Approval no. XJZ-LL-2024-051). Written informed consent was obtained from a legally authorized representatives for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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