TGF- β 1 and Its Signal Transduction Pathways: Are They Corelated With The Elastic Characteristics of Breast Lesions?

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Abstract

Background: Shear wave elastography (SWE) can evaluate the tissue stiffness. Previous studies showed that the elastic characteristics of breast lesions were related to the components of extracellular matrix (ECM) which was directly or indirectly regulated by transforming growth factor beta 1 (TGF- β 1). However, it is rarely reported whether there is a correlation between TGF- β 1 and the elastic characteristics of breast lesions. The purpose of this study was to investigate the relationship between TGF- β 1 with its signal transduction pathways and the elastic characteristics of breast lesions.

Methods: 135 breast lesions in 130 patients were included. Before operation or biopsy, SWE was performed. Elastic characteristics such as the maximum, mean, minimum and standard deviation (SD) of elastic modulus (Emax, Emean, Emin, Esd), the elastic ratio of the lesions to the peripheral tissue (Eratio) and the "stiff rim sign" were recorded. The expression levels of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT were detected by immunohistochemistry. The elastic characteristics and the expression levels of the above-mentioned indexes of benign lesions were analyzed.

Results: Emax, Emean, Esd, Eratio, "stiff rim sign" detection rate and the expression levels of TGF- β 1, et al. of benign were lower than those of malignant lesions ($P \leq 0.0001$). The expression levels of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT were correlated with Emax, Emean, Esd, Eratio of breast lesions, the expression levels of TGF- β 1, et al. of lesions with "stiff rim sign" were higher than those of lesions without "stiff rim sign" ($P \leq 0.05$). And the expression levels of Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT were correlated with that of TGF- β 1 ($r = 0.678, 0.633, 0.645, 0.611, 0.589, 0.663, P \leq 0.0001$).

Conclusions: The expression levels of TGF- β 1, et al. of breast lesions were correlated with the elastic characteristics, the expression levels of Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT were correlated with that of TGF- β 1, which speculated that TGF- β 1 might play an important role in the stiffness regulation of breast lesions through multiple signal transduction pathways.

Introduction

Breast cancer is the most common malignant epithelial tumor in women with the highest fatality rate in female cancerous lesions[1]. With the rapid development of economy and society, China has become one of the countries with the fastest increasing incidence of breast cancer in the world[2]. Therefore, the situation of breast cancer in China is grim, which seriously endangers the physical and mental health of women. Studies have shown that early detection and early diagnosis of breast cancer have more significant therapeutic and prognostic effects[3, 4]. Therefore, how to early detect and diagnose breast cancer early has become a problem that long been expected to be solved by multiple examination methods.

At present, mammography is widely used as the main tool and ultrasound as the supplemental tool for screening breast lesions. However, mammography is limited by dense breast tissue, resulting in reduced sensitivity[5]. Previous studies have shown that increased breast density is an independent risk factor for breast cancer[6]. Ultrasound, which can overcome the limitation of breast density, has gradually begun to be recognized, and its application is becoming more and more widespread. Shear wave elastography (SWE) is a new ultrasound technology based on conventional ultrasound, which quantifies the tissue stiffness information with specific numerical values[7]. And its value in differential diagnosis of benign and malignant breast lesions has been proved by many studies[7-9].

Previous studies shown that the elastic characteristics of breast lesions were related to the components of extracellular matrix (ECM), and collagen and elastin in ECM were important factors that determine the elasticity of breast lesions[10, 11]. While the changes of composition and structure of ECM are mainly regulated by transforming growth factor β (TGF- β) [12, 13].

TGF- β is widely distributed in human body, and TGF- β 1 is the most abundant. It can regulate the processes of cell carcinogenesis, proliferation, differentiation, apoptosis, metabolism and growth through TGF- β 1/Smad, TGF- β 1/MAPK, PI3K/AKT and other signal transduction pathways, and participate in almost the whole process of occurrence, development, invasion and metastasis of breast lesions[14-16]. In addition, TGF- β 1 can directly or indirectly promote the excessive deposition of collagen and fibrin in ECM, and inhibit the degradation of ECM, resulting in the increase of ECM stiffness[17-19]. Therefore, TGF- β 1, ECM and elastic characteristics of breast lesions are closely related.

However, it is rarely reported whether there is a correlation between TGF- β 1 and the elastic characteristics of breast lesions, and it is urgent to explore whether the indexes of TGF- β 1 signal transduction pathway are related to the elastic characteristics of breast lesions. Therefore, the purpose of this study was to investigate the relationship between TGF- β 1 with its signal transduction pathways and the elastic characteristics of breast lesions.

Materials And Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical ethics committee of our hospital (No. S2020-336-01), and written informed consent was obtained from all patients.

135 breast lesions in 130 patients who underwent surgical excision, ultrasound-guided vacuum-assisted biopsy (VAB) or core needle biopsy (CNB) after SWE examinations were included in the study from March 2018 to October 2018. The age of the patients ranged from 18 to 73 years old, with an average of (44 ± 12) years, and the maximum diameter of the lesion ranged from 0.5 to 13.9 cm, with an average of (2.1 ± 1.5) cm. The pathological result confirmed by VAB or surgery was considered as "gold standard". Then the axillary lymph node metastasis of patients with malignant breast lesions was followed up.

A number of criteria were considered when including patients: I. Pathological results obtained by VAB or surgical excision; II. Clear and definite pathological diagnosis; III. Lesions haven't undergone neoadjuvant chemotherapy or radiotherapy; IV. No serious diseases of heart, lung, liver, kidney, etc. or malignant lesions; V. Patients can tolerate biopsy or surgical excision procedure; VI. Comprehensive information of clinical, ultrasound, pathology prognosis and follow-up; VII. Written informed consent was obtained.

SWE examination

Aixplorer ultrasound system (SuperSonic Imagine, Aix en Provence, France) with a L15-4 linear array probe was used for SWE examination. Ultrasound examination was performed at the site of the lesion firstly, and the best section to show the lesion was selected, and then switched to the SWE mode. Keep the patient to breathe smoothly, and the probe was placed at the site of the lesion with no pressure for 3 seconds to stabilize the image, then froze and store it. And after that the region of interest (ROI) was chosen. When choosing ROI, try to keep ROI to cover all parts of the lesion, especially the stiffest part. Then the maximum elastic modulus (Emax), mean elastic modulus (Emean), minimum elastic modulus (Emin), the standard deviation of elastic modulus (Esd) was recorded, and the elasticity ratio (Eratio) of the lesion shown by ROI to the peripheral normal breast tissue at the same depth was also recorded. Repeat the above steps in five different sections of the lesion. Calculate and record the mean value of Emax, Emean, Emin, Esd and Eratio in these five sets of data. Besides, the appearance of the red area of increased stiffness with or without open or closed ring at the edge of the lesion ("stiff rim sign") was observed.

Immunohistochemistry

The samples were fixed in formalin and embedded in paraffin, and then cut into sections with a thickness of 4 μ m, and then TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT expression was evaluated by immunohistochemistry. Image-Pro Plus 6.0 was used for semi-quantitative analysis of immunohistochemical results. Five ROIs were randomly selected from each sample under the 400x field of view and photographed to measure the integrated optical density (IOD) and area. The yellow area is the positive expression area. Expression levels of TGF- β 1 and other factors were expressed by average optical density (IOD/area).

Statistical analysis

SPSS 26.0, standard version (SPSS Inc., Chicago, IL, USA) statistical software was used for statistical analysis. The quantitative data were expressed as ($\bar{x} \pm s$) and the qualitative data were expressed as %. Student's t test was used to compare the differences between groups of quantitative data, and χ^2 test was used to compare the differences of qualitative data. Taking the pathological results as the "gold standard", the receiver operator characteristic curve (ROC) of each factor were drawn respectively, and the efficacy was evaluated by the area under the curve (AUC), and the cutoff value, sensitivity and specificity were analyzed, and the differences among AUC were compared by Z test. Spearman rank correlation test was used for correlation analysis. $P \leq 0.05$ was considered as the difference was statistically significant.

Results

Pathological results

Of the 135 breast lesions, 84 (62.2%, 84/135) were benign, including 32 fibroadenomas, 40 adenosis, 3 intraductal papillomas, 8 inflammatory lesions, 1 benign phyllodes tumor, and 51 (37.8%, 51/135) were malignant, among them, there were 46 invasive carcinomas, 3 intraductal carcinomas and 2 mucinous carcinomas.

Analysis of elastic characteristics of breast lesions

The elastic characteristics of benign and malignant breast lesions were seen in Table 1, Figure 1A and Figure 2A. The Emax, Emean, Esd and Eratio of benign breast lesions was significantly lower than those of malignant lesions ($P < 0.001$), but there was no significant difference in Emin between benign and malignant breast lesions ($P = 0.202$). Besides, the detection rate of "stiff rim sign" in malignant lesions was significantly higher than that of benign lesions ($P < 0.001$).

Expression levels of TGF- β 1 and other factors in breast lesions

The expression levels of TGF- β 1 and other factors in breast lesions were seen in Table 2, Figure 1B~H and Figure 2B~H. Immunohistochemical staining showed that TGF- β 1 and PI3K were mainly expressed in the cytoplasm, while Smad2/3, Erk1/2, p38 MAPK, JNK2 and AKT were mainly expressed in the cytoplasm and nucleus. And the expression levels of TGF- β 1 and other factors in malignant breast lesions were significantly higher than those in benign lesions ($P < 0.001$).

When using the expression levels of TGF- β 1 and other factors as an index respectively for the differential diagnosis of benign and malignant breast lesions, the ROC curve was shown in Figure 3, the AUC were 0.931 (0.874-0.967), 0.953 (0.901-0.982), 0.920 (0.861-0.960), 0.957 (0.902-0.986), 0.934 (0.874-0.971), 0.960 (0.901-0.989) and 0.939 (0.883-0.974), respectively. Z test showed that there was no significant difference among the seven groups ($P > 0.05$). When the cutoff value of the average optical density of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT was > 0.2175 , > 0.1496 , > 0.2036 , > 0.1447 , > 0.1583 , > 0.2624 , > 0.1230 respectively, the sensitivity and specificity for differential diagnosis of benign and malignant breast lesions were 90.0% and 88.2%, 93.9% and 90.2%, 80.0% and 89.4%, 89.1% and 95.5%, 90.2% and 85.0%, 93.6% and 94.4%, 80.0% and 89.4%, respectively.

Correlation analysis

The correlation between the expression levels of TGF- β 1 and other factors and elastic characteristics in breast lesions was shown in Figure 4~7. Spearman test showed that the expression levels of TGF- β 1 and other factors were positively correlated with Emax, Emean, Esd and Eratio in breast lesions (correlation coefficient 0.879, 0.595, 0.571, 0.562, 0.516, 0.552, 0.619 for Emax, 0.841, 0.549, 0.503, 0.504, 0.516, 0.542, 0.578 for Emean, 0.865, 0.580, 0.566, 0.593, 0.514, 0.559, 0.649 for Esd and 0.746, 0.510, 0.507, 0.506, 0.536, 0.511, 0.550 for Eratio, $P=0.0001$).

Expression levels of TGF- β 1 and other factors in breast lesions with and without "stiff rim sign" could be seen in Table 3. Immunohistochemical staining showed that the expression levels of TGF- β 1 and other factors in breast lesions with "stiff rim sign" were significantly higher than those in breast lesions without "stiff rim sign" ($P=0.001$).

The correlation between the expression levels of TGF- β 1 and other factors in breast lesions was shown in Figure 8. Spearman test showed that the expression levels of Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT were positively correlated with TGF- β 1 in breast lesions (correlation coefficient 0.678, 0.633, 0.645, 0.611, 0.589, 0.663, $P=0.0001$).

Axillary lymph node metastasis

Expression levels of TGF- β 1 and other factors in malignant breast lesions with and without axillary lymph node metastasis could be seen in Table 4. The difference between malignant breast lesions with axillary lymph node metastasis and malignant breast lesions without axillary lymph node metastasis lied in that the expression levels of TGF- β 1 and other factors of former were significantly higher than those of the latter ($P < 0.05$).

Basing on the expression levels of TGF- β 1 and other factors in malignant breast lesions, ROC curves of which for differential diagnosis of malignant breast lesions with and without axillary lymph node metastasis were shown in Figure 9. The AUC were 0.853 (0.703-0.946), 0.697 (0.529-0.834), 0.694 (0.527-0.832), 0.706 (0.531-0.845), 0.654 (0.466-0.813), 0.667 (0.493-0.813) and 0.689 (0.516-0.831), respectively. When the expression levels of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT were cut off by average optical density > 0.3138 , > 0.2679 , > 0.2457 , > 0.2812 , > 0.2760 , > 0.3075 , > 0.2348 respectively, the sensitivity and specificity for differential diagnosis of malignant breast lesions with or without axillary lymph node metastasis were 86.7% and 83.3%, 80.0% and 62.5%, 80.0% and 58.3%, 69.2% and 65.2%, 50.0% and 80.0%, 86.7% and 40.9%, 42.9% and 91.3%, respectively.

Quantile regression analysis

As shown in Table 5~8, the percentile regression analysis was performed with the expression levels of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT in breast lesions as independent variables and Emax, Emean, Esd and Eratio as target variables respectively. At different quantiles, only the expression level of TGF- β 1 always had a significant positive effect on Emax, Emean, Esd and Eratio, while Smad2/3 only had a certain effect on Emean at the point of 0.75th quartile, a negative effect on Eratio at the point of 0.45th quartile. Erk1/2 only had a certain effect on Emean at the 0.75th quartile. That is, the expression level of TGF- β 1 is the most important factor to determine the Emax, Emean, Esd and Eratio of breast lesions.

Logistic regression analysis

Taking the expression levels of TGF- β 1, Smad2/3, Erk1/2, p38MAPK, JNK2, PI3K and AKT in breast lesions as independent variables and "stiff rim sign" as dependent variable, logistic regression analysis was performed. The logistic regression equation was established as follows:

$$\text{Logit}(P) = -5.977 - 17.049 X_1$$

X_1 represented the expression level of TGF- β 1, that is, the expression level of TGF- β 1 was the main factor determining the presence or absence of "stiff rim sign", as shown in Table 9.

Discussion

SWE could quantitatively evaluate the elastic characteristics of breast lesions and more accurately judge the benign and malignant breast lesions. Our study showed that there were significant differences in elastic characteristics between benign and malignant breast lesions, which were the same as those of previous studies[8, 20]. For malignant breast lesions, a large number of cancer cells proliferated, invaded and infiltrated the normal breast stroma and adipose tissue, and interacted with the tumor microenvironment, causing complex connective tissue hyperplasia and fibrosis, which were important typical pathological changes in the process of tumor development and invasion, they could lead to overexpression and accumulation of ECM components, rearrangement and cross-linking of ECM structure[21, 22], and increase the stiffness of the lesions. At the same time, the proliferation and fibrosis of connective tissue caused by the continuous invasion of cancer cells made the fibroblasts grow to the edge of the lesion[23], according to the number of collagen and elastic fibers and the degree of fibrosis, the lesions exerted different degrees of tension on the surrounding tissue[24], and elastin and fibrin would harden under stretching[25], thus increasing the stiffness of the tissue around the lesion by 2-10 times. As a result, the "stiff rim sign" appeared.

Our study found that the expression levels of TGF- β 1 and other factors in malignant breast lesions were significantly higher than those in benign breast lesions. It was not difficult to understand such results. TGF- β had both inhibitory and promoting effects on tumor cells[26]. In the early stage of tumorigenesis, TGF- β could induce tumor cell apoptosis and inhibit tumor growth through the TGF- β /Smad signal pathway, but with the occurrence and development of tumor, most cancer cells could secrete TGF- β , and the elevated level of TGF- β could promote the occurrence and development of tumor[27]. The proliferation and invasion of cancer cells led to the activation of TGF- β 1 and the increase of TGF- β 1 expression, which affected the growth of cancer

cells and promoted the transformation of normal fibroblasts into cancer associated fibroblasts (CAFs)[28, 29]. CAFs could interact with cancer ECM to promote the growth, development, invasion and metastasis of cancer, thus further increasing the expression level of TGF- β 1. For TGF- β 1 could participate in almost the whole process of occurrence, development, invasion and metastasis of breast lesions through TGF- β 1/Smad, TGF- β 1/MAPK, PI3K/AKT and other signal transduction pathways, the expression levels of TGF- β 1 and other factors in malignant breast lesions were naturally higher than those in benign lesions. These also explained another result of this study: the expression levels of TGF- β 1 and other factors in malignant breast lesions with or without axillary lymph node metastasis were significantly different.

The study also showed that the expression levels of TGF- β 1 and other factors in breast lesions had a certain value in the differential diagnosis of benign and malignant breast lesions, suggesting that TGF- β 1 and other factors might be used as new indexes for differential diagnosis of benign and malignant breast lesions and new breakthrough points for clinical diagnosis and treatment.

In our study, the expression level of TGF- β 1 was found to be correlated with Emax, Emean, Esd, Eratio, and the expression level of TGF- β 1 in breast lesions with "stiff rim sign" was significantly higher than those in breast lesions without "stiff rim sign". According to the previous studies, on the one hand, TGF- β 1 could promote the activation and production of CAFs. CAFs mainly synthesizes and secretes ECM proteins and proteins related to ECM remodeling, which in turn promotes the excessive accumulation of ECM components and the remodeling of ECM structure[18, 29, 30]. On the other hand, TGF- β 1 could directly stimulate the synthesis and cross-linking rearrangement of collagen, elastin and laminin, and inhibit the activity of enzymes that degrade ECM components to inhibit their degradation, lead to excessive accumulation of ECM components and structural changes of ECM, and increased ECM stiffness[22, 31]. In addition, TGF- β 1 could also improve cell adhesion by promoting cancer cell synthesis and secretion of a variety of proteases, resulting in cancer cells adhering to the surrounding breast stroma and adipose tissue, resulting in reduced lesion activity and increased lesion stiffness[32].

In the process of carcinogenesis and development, the signal transmitted by TGF- β 1 could be transmitted to the nucleus through TGF- β 1/Smad signal pathway, on one hand, it could directly up-regulate the expression of collagen fibers[33], and on the other hand, it could induce the process of epithelial-mesenchymal transformation (EMT). EMT could upregulate the expression of ECM components such as collagen and fibronectin[16], and thus increase the stiffness of ECM. Cancer cells could produce oxidative stress in the process of differentiation and invasion, and reactive oxygen species could promote the initiation of TGF- β 1/Smad signal transduction pathway, hinder the degradation of fibrin, make fibrin deposition[34], and lead to the stiffening of ECM. Similarly, the increased expression of TGF- β 1 could also induce the occurrence of EMT process by activating MAPK signal transduction pathway and PI3K/AKT/mTOR signal transduction pathway[16], which increased the stiffness of ECM and leads to the stiffening of lesions. And with the increase of ECM stiffness, the signal transduction of PI3K/AKT pathway can be activated and enhanced[35]. Therefore, it is not difficult to understand the correlation between the expression levels of Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K, AKT and Emax, Emean, Esd, Eratio, "stiff rim sign" in this study.

The study also found that the expression levels of Smad2/3, Erk1/2, p38MAPK, JNK2, PI3K and AKT in breast lesions were correlated with that of TGF- β 1, which further suggested that TGF- β 1 might indeed participate in almost the whole process of occurrence, development, invasion and metastasis of breast lesions through signal transduction pathways such as TGF- β 1/Smad, TGF- β 1/MAPK, PI3K/AKT.

One of the important factors affecting the prognosis and 5-year survival time of patients with malignant breast lesions was whether the disease had lymph node metastasis, especially axillary lymph node metastasis[36]. Our study showed that the expression levels of TGF- β 1 and other factors in malignant breast lesions had a certain value in predicting whether malignant breast lesions had axillary lymph node metastasis or not, which suggested that the presence or absence of axillary lymph node metastasis in malignant breast lesions might be evaluated according to the expression levels of TGF- β 1 and other factors, it is of great significance for axillary lymph node dissection in the clinical operation of malignant breast lesions.

It was also found in the study that the expression level of TGF- β 1 was the main factor affecting the elastic characteristics of breast lesions, such as Emax, Emean, Esd, Eratio, and the expression level of TGF- β 1 was the independent risk factor for the presence of "stiff rim sign", which suggested that TGF- β 1 might play an important role in the regulation of elastic characteristics of breast lesions, or it might become a new breakthrough point for differential diagnosis of benign and malignant breast lesions and a potential target for treatment.

There are some limitations in this study. In this study, the main components of ECM such as collagen fibers and elastic fibers were not detected, so the relationships between collagen fibers, elastic fibers and the expression levels of TGF- β 1 and other factors and the elastic characteristics of breast lesions were not analyzed, so as to further explore whether TGF- β 1 regulates the stiffness of breast lesions by regulating ECM, and whether conventional ultrasound features were related to the expression levels of TGF- β 1 and other factors were not analyzed, either. Therefore, the next step is to carry out the above two aspects of research, in order to make the study more in-depth and comprehensive.

In conclusion, the expression levels of TGF- β 1 and other factors in breast lesions were correlated with Emax, Emean, Esd, Eratio, "stiff rim sign" and axillary lymph node metastasis, and the expression level of TGF- β 1 was the main factor affecting the Emax, Emean, Esd, Eratio, "stiff rim sign", the expression levels of Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT were also correlated with the expression level of TGF- β 1, which speculated that TGF- β 1 might play an important role in the stiffness regulation of breast lesions through multiple signal transduction pathways.

Abbreviations

SWE: Shear wave elastography

ECM: extracellular matrix

TGF- β : transforming growth factor β

VAB: vacuum-assisted biopsy

CNB: core needle biopsy

ROI: region of interest

IOD: integrated optical density

ROC: receiver operator characteristic curve

AUC: area under the curve

CAFs: cancer associated fibroblasts

EMT: epithelial-mesenchymal transformation

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical ethics committee of China PLA General Hospital (No. S2020-336-01), and written informed consent was obtained from all patients.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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Authors' contributions

Z.L.W. and G. L. designed the work; M.K.Z. and B. W. the acquisition, analysis;

1. Y. L and B. W. collected and interpreted data;

M.K.Z. and S. Y. L prepared all figures;

M.K.Z. have drafted the work;

Z.L.W. and G. L. made critical revision of the manuscript for important intellectual content.

All authors reviewed the manuscript.

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Tables

Table 1 Comparison of elastic characteristics between benign and malignant breast lesions

Factors	Benign lesions (n=84)	Malignant lesions (n=51)	t (t')/χ ²	P
E _{max} (kPa)*	58.2±50.5	161.9±79.5	9.276	0.001
E _{mean} (kPa)*	35.9±26.4	99.6 ± 51.9	9.433	0.001
E _{min} (kPa)	15.4±12.9	20.6 ± 19.5	1.287	0.202
E _{sd} (kPa)*	8.9±7.9	30.1±17.5	9.011	0.001
E _{ratio} *	2.1±1.7	6.0 ± 4.1	7.625	0.001
Stiff rim sign [n(%)]*	4(4.8)	38(74.5)	72.030	0.001

*statistical significance.

Table 2 Comparison of expression levels of TGF-β1 and other factors between benign and malignant breast lesions (x ±s)

Factors	Benign lesions (n=84)	Malignant lesions (n=51)	t (t')	P
TGF-β1 *	0.1038±0.0092	0.2995±0.01114	13.300	0.001
Smad2/3*	0.0745±0.0497	0.2511±0.0754	16.160	0.001
Erk1/2 *	0.1242±0.0552	0.2547±0.0667	12.300	0.001
p38 MAPK*	0.0459±0.0516	0.2613±0.0914	15.930	0.001
JNK2*	0.1101±0.0549	0.2558±0.0720	12.450	0.001
PI3K *	0.1240±0.0702	0.3425±0.0608	16.640	0.001
AKT *	0.0741±0.0546	0.2166±0.0679	13.070	0.001

*statistical significance.

Table 3 Comparison of expression levels of TGF-β1 and other factors in breast lesions with and without "stiff rim sign" (x ±s)

Factors	Stiff rim sign		t (t')	P
	Yes(n=42)	None(n=93)		
TGF-β1*	0.3090±0.0682	0.1164±0.0960	11.720	0.001
Smad2/3*	0.2332±0.0981	0.1004±0.0792	8.242	0.001
Erk1/2*	0.2441±0.0831	0.1416±0.0683	7.539	0.001
p38 MAPK*	0.2429±0.1116	0.0832±0.0998	7.673	0.001
JNK2*	0.2429±0.0875	0.1285±0.0729	7.321	0.001
PI3K*	0.3212±0.0954	0.1692±0.1096	7.130	0.001
AKT*	0.2025±0.0886	0.0945±0.0712	7.332	0.001

*statistical significance.

Table 4 Comparison of expression levels of TGF- β 1 and other factors in malignant breast lesions with and without axillary lymph node metastasis (x $\pm$ s)

Factors	Metastasis		t (t')	P
	Yes(n=15)	None(n=36)		
TGF- β 1 *	0.3204 $\pm$ 0.0381	0.2648 $\pm$ 0.0650	2.999	0.0048
Smad2/3*	0.2956 $\pm$ 0.0251	0.2513 $\pm$ 0.0628	2.592	0.0136
Erk1/2 *	0.2814 $\pm$ 0.0609	0.2414 $\pm$ 0.0553	2.118	0.0410
p38 MAPK*	0.2999 $\pm$ 0.0506	0.2484 $\pm$ 0.0759	2.180	0.0363
JNK2*	0.2832 $\pm$ 0.0627	0.2415 $\pm$ 0.0507	2.063	0.0478
PI3K *	0.3396 $\pm$ 0.0316	0.3110 $\pm$ 0.0459	2.094	0.0436
AKT *	0.2225 $\pm$ 0.0716	0.1704 $\pm$ 0.0713	2.154	0.0382

*statistical significance.

Table 5 Percentile regression analysis results of Emax and the expression levels of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT

Factors	Percentiles									
	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
Constant	0.879 (0.065)	9.246 (0.787)	5.892 (0.725)	2.208 (0.219)	5.293 (0.520)	8.165 (0.954)	4.873 (0.549)	7.216 (0.773)	6.928 (0.761)	12.269 (0.970)
TGF- β 1	246.281 (4.088**)	394.203 (7.519**)	481.854 (13.296**)	508.789 (11.315**)	575.917 (12.679**)	593.743 (15.561**)	629.329 (15.912**)	637.585 (15.305**)	624.232 (15.366**)	838.401 (14.859**)
Erk1/2	120.037 (1.417)	17.122 (0.232)	37.736 (0.740)	35.942 (0.568)	5.311 (0.083)	8.878 (0.165)	7.135 (0.128)	-19.103 (-0.326)	10.072 (0.176)	-28.314 (-0.357)
Smad2/3	- 74.443(1.113)	-16.223 (-0.223)	-66.575 (-1.322)	2.282 (0.037)	35.236 (0.558)	22.914 (0.432)	56.750 (1.033)	98.069 (1.940)	92.868 (1.859)	9.671 (0.123)
AKT	76.114 (1.115)	23.651 (0.364)	-4.522 (-0.101)	-37.059 (-0.665)	-33.669 (-0.598)	-47.726 (-1.009)	-45.340 (-0.924)	-46.166 (-0.893)	1.183 (0.023)	6.457 (0.092)
PI3K	-59.305 (-0.800)	-61.242 (-0.950)	-57.044 (-1.280)	-26.049 (-0.471)	-34.215 (-0.613)	-11.215 (-0.239)	16.930 (0.348)	9.701 (0.189)	-4.563 (-0.091)	23.487 (0.338)
MAPK	-69.315 (-1.103)	4.674 (0.086)	-17.941 (-0.475)	-20.672 (-0.441)	2.370 (0.050)	37.668 (0.947)	45.589 (1.106)	22.639 (0.521)	-44.900 (-1.060)	-2.834 (-0.048)
JNK2	34.819 (0.475)	-3.160 (-0.050)	19.572 (0.444)	18.803 (0.344)	-20.441 (-0.370)	-72.192 (-1.556)	-65.744 (-1.299)	-94.286 (-1.861)	-88.809 (-1.850)	-130.496 (-1.902)

Note: the values in parentheses were t value, * $P \leq 0.05$ ** $P \leq 0.01$

Table 6 Percentile regression analysis results of Emean and the expression levels of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT

Factors	Percentiles									
	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
Constant	2.515 (2.764**)	5.153 (0.614)	5.302 (0.607)	3.906 (0.535)	5.219 (0.937)	7.044 (1.129)	8.812 (1.174)	12.887 (1.893)	19.159 (2.447*)	52.857 (3.331**)
TGF-β1	165.740 (40.847**)	272.166 (7.273**)	275.848 (7.078**)	306.187 (9.404**)	311.012 (12.523**)	330.379 (11.878**)	331.917 (9.913**)	348.870 (11.493**)	396.475 (11.353**)	283.164 (4.001**)
Erk1/2	9.134 (1.869)	27.242 (0.518)	5.337 (0.097)	-19.645 (-0.429)	-14.899 (-0.427)	-26.436 (-0.676)	-62.152 (-1.320)	-89.939 (-2.107*)	-70.397 (-1.434)	-137.854 (-1.385)
Smad2/3	-10.401 (-1.948)	-29.460 (-0.590)	28.310 (0.523)	59.515 (1.316)	48.011 (1.391)	74.255 (1.921)	34.924 (0.900)	149.744 (3.550**)	87.728 (1.808)	167.575 (1.738)
AKT	6.943 (1.198)	58.972 (1.271)	-13.985 (-0.289)	-40.210 (-0.996)	4.966 (0.161)	13.972 (0.405)	-5.790 (-1.139)	-41.723 (-1.108)	-20.310 (-0.469)	-117.021 (-1.333)
PI3K	-9.712 (-1.911)	-15.839 (-0.344)	-26.241 (-0.548)	2.051 (0.051)	-16.296 (-0.534)	-22.552 (-0.659)	-35.817 (-0.870)	-50.265 (-1.347)	-63.175 (-1.471)	-176.770 (-1.761)
P38 MAPK	-8.844 (-1.818)	-2.021 (-0.052)	10.735 (0.264)	-18.712 (-0.551)	-6.704 (-0.259)	-6.008 (-0.207)	9.940 (0.285)	43.607 (1.378)	85.537 (2.349)	191.916 (1.836)
JNK2	9.514 (1.901)	-30.758 (-0.676)	-15.982 (-0.337)	1.976 (0.050)	-9.354 (-0.310)	-22.872 (-0.676)	8.012 (0.197)	33.942 (0.920)	-13.712 (-0.323)	28.135 (0.327)

Note: the values in parentheses were t value, * $P \leq 0.05$ ** $P \leq 0.01$

Table 7 Percentile regression analysis results of Esd and the expression levels of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT

Factors	Percentiles									
	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
Constant	0.527 (0.474)	-0.714 (-0.311)	0.367 (0.156)	-0.120 (-0.049)	-2.526 (-0.757)	-2.043 (-0.624)	-1.405 (-0.423)	-2.446 (-0.703)	-2.194 (-0.503)	-2.805 (-0.042)
TGF-β1	22.480 (4.946**)	70.439 (7.503**)	63.092 (6.578**)	75.920 (7.501**)	109.328 (8.017**)	113.801 (8.509**)	112.599 (8.286**)	104.303 (7.337**)	132.677 (7.440**)	117.040 (2.217*)
Erk1/2	12.786 (1.758)	-12.731 (-0.891)	-9.527 (-0.653)	-10.331 (-0.671)	-2.835 (-0.137)	-10.140 (-0.498)	-6.910 (-0.334)	-4.137 (-0.191)	5.001 (0.184)	18.186 (0.407)
Smad2/3	-10.225 (-1.492)	-25.332 (-1.886)	-4.195 (-0.306)	0.339 (0.023)	1.619 (0.083)	7.046 (0.368)	19.713 (1.014)	31.167 (1.532)	12.837 (0.503)	81.503 (1.912)
AKT	11.152 (1.653)	-3.635 (-0.322)	2.482(0.215)	1.541 (0.127)	-3.895 (-0.237)	-7.848 (-0.488)	-11.279 (-0.690)	13.315 (0.779)	2.485 (0.116)	-2.034 (-0.37)
PI3K	-6.335 (-1.163)	6.578 (0.585)	-0.590 (-0.051)	3.185 (0.263)	10.962 (0.671)	17.097 (1.067)	16.826 (1.033)	19.973 (1.172)	14.122 (0.661)	13.965 (0.319)
P38 MAPK	5.410 (1.138)	13.940 (1.374)	10.201 (0.984)	11.205 (1.024)	10.597 (0.719)	11.347 (0.785)	12.809 (0.872)	1.537 (0.100)	-18.073 (-0.938)	-49.386 (-1.073)
JNK2	-11.226 (1.490)	7.915 (0.673)	5.724 (0.477)	-2.051 (-0.162)	-12.575 (-0.736)	-15.636 (-0.934)	-24.628 (-1.447)	-18.915 (-1.062)	9.965 (0.446)	22.565 (0.472)

Note: the values in parentheses were t value, * $P \leq 0.05$ ** $P \leq 0.01$

Table 8 Percentile regression analysis results of Eratio and the expression levels of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT

Factors	Percentiles									
	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
Constant	-0.058 (-0.079)	-0.586 (-0.946)	0.045 (0.077)	0.087 (0.182)	0.319 (0.687)	0.695 (0.980)	0.226 (0.284)	0.080 (0.136)	-0.119 (-0.035)	4.236 (0.441)
TGF- β 1	13.933 (4.601**)	6.751 (2.509*)	11.378 (4.419**)	14.082 (6.820**)	15.654 (7.768**)	14.928 (4.840**)	15.123 (4.366**)	18.126 (7.125**)	19.985 (7.339**)	110.466 (7.731**)
Erk1/2	2.771 (0.608)	6.286 (1.648)	0.249 (0.068)	-0.499 (-0.170)	-3.591 (-1.257)	-3.766 (-0.861)	-3.841 (-0.782)	-0.037 (-0.01)	0.913 (0.043)	-39.144 (-0.662)
Smad2/3	-6.359 (-1.417)	-5.757 (-1.533)	-4.420 (-1.230)	-3.594 (-1.247)	-6.242 (-2.219*)	-6.249 (-1.451)	-2.435 (-0.504)	-4.113 (-1.158)	-5.014 (-0.241)	44.481 (0.764)
AKT	5.978 (1.500)	3.844 (1.152)	1.196 (0.375)	0.376 (0.147)	2.971 (1.189)	3.361 (0.878)	3.160 (0.736)	2.215 (0.702)	3.831 (0.207)	-15.238 (-0.295)
PI3K	-1.496 (-0.378)	-0.647 (-1.196)	2.862 (0.904)	3.808 (1.500)	3.338 (1.234)	3.905 (1.209)	5.633 (1.322)	5.043 (1.612)	4.127 (0.225)	-13.009 (-0.254)
P38	-2.112 (-0.630)	0.385 (0.137)	-1.337 (-0.498)	-1.521 (-0.706)	-2.104 (-1.001)	-0.774 (-0.241)	-2.010 (-0.557)	-0.933 (-0.352)	-2.056 (-0.132)	5.076 (0.117)
MAPK										
JNK2	5.940 (1.503)	2.384 (0.721)	1.748 (0.552)	0.377 (0.149)	1.763 (0.712)	2.336 (0.616)	4.779 (1.122)	3.031 (0.969)	5.463 (0.298)	26.230 (0.511)

Note: the values in parentheses were t value, * $P \leq 0.05$ ** $P \leq 0.01$

Table 9 The results of logistic regression analysis for determining the presence or absence of "stiff rim sign"

Factors	B	S.E.	Wald	P	OR	OR 95%CI
TGF- β 1*	17.049	5.005	11.602	0.001	25372088.366	1392.462-462305423321.366
Constant *	-5.977	1.501	15.851	0.000	0.003	-

Figures

Figure 1

SWE and immunohistochemical images of invasive breast cancer in a 38-year-old woman. A: SWE showed that the Emax was 226.0 kPa, the Emean was 159.3 kPa, the Estd was 37.4 kPa, and the Eratio was 20.0, and the "stiff rim sign" (the white arrow) can be seen; B~H: Immunohistochemical staining

showed that the expression of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT was strong or moderate positive, and the average optical density was 0.349, 0.342, 0.355, 0.172, 0.296, 0.373, 0.324, respectively ($\times 400$).

Figure 2
SWE and immunohistochemical images of breast fibroadenoma in a 36-year-old woman. A: SWE showed that the Emax was 6.3 kPa, the Emean was 4.3 kPa, the Esd was 1.1 kPa, and the Eratio was 0.6; B~H: Immunohistochemical staining showed that the expression of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT was weak positive, and the average optical density was 0.012, 0.078, 0.032, 0.022, 0.050, 0.090, 0.099, respectively ($\times 400$).

Figure 3
ROC curves of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT expression levels in breast lesions for differential diagnosis of benign and malignant breast lesions.

Figure 4

Correlations of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT expression with Emax.

Figure 5

Correlations of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT expression with Emean.

Figure 6

Correlations of TGF-β1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT expression with Esd.

Figure 7

Correlations of TGF-β1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT expression with Eratio.

Figure 8

Correlations of Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT expression with TGF- β 1.

Figure 9

ROC curves of TGF- β 1, Smad2/3, Erk1/2, p38 MAPK, JNK2, PI3K and AKT expression levels in malignant breast lesions for differential diagnosis of malignant breast lesions with and without axillary lymph node metastasis