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ORIGINAL ARTICLE

Evaluation of the value of GATA3 combined with E-cadherin in the diagnosis of breast cancer

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Summary

Purpose: *To analyze the clinical value of GATA-3 combined with E-cadherin in the diagnosis of breast cancer.*

Methods: *120 patients with breast cancer treated in Affiliated Tumor Hospital of Guangxi Medical University for the first time (experimental group) from May 2014 to December 2016 and 80 healthy females (control group) were retrospectively analyzed. The expression levels of GATA3 and E-cadherin in the experimental group and the control group were detected by enzyme-linked immunosorbent assay (ELISA). Binary logistic regression analysis was used to evaluate the combined detection of GATA3 and E-cadherin, and the value of GATA3 and E-cadherin single diagnosis and their combined diagnosis in patients with breast cancers was compared.*

Results: *The expression levels of GATA3 and E-cadherin in breast cancer patients were correlated with clinical stage, human epidermal growth factor receptor 2 (HER-2), estrogen (ER) and progesterone receptor (PR) ($p<0.05$). The expression level of GATA3 in the experimental group was significantly higher than that in the control group ($p<0.01$), and the expression level of E-cadherin in the experimental group was significantly lower than that in the control group ($p<0.01$). GATA3 was highly expressed in breast cancer patients before surgery and decreased significantly after surgery ($p<0.01$). E-cadherin was lowly expressed in breast cancer patients before surgery and increased significantly after surgery ($p<0.01$).*

Conclusion: *Combined detection of GATA3 and E-cadherin is of great significance in the diagnosis and treatment of breast cancer, and it is expected to become an effective indicator for the diagnosis of breast cancer in the future.*

Key words: *GATA3, E-cadherin, breast cancer, diagnosis*

Introduction

With the continuous development of social life, changes in lifestyle and dietary habits along with the deteriorating environment, breast cancer has become the malignancy with the highest incidence in females [1], which seriously affect people's physical, family and mental health. In 2013, there were approximately 234,580 new cases of breast cancer in the United States, with a death toll of about 40030 [2]. It is predicated that there will be more than 100 cases of breast cancer per 100 000 women by 2021 in China [3]. Therefore, early detection and diagnosis of breast cancer is the key to improving the therapeutic results [4]. Tumors and normal tissues have significant differences in gene expression patterns, so tumors can be diagnosed by detecting specific proteins in blood and tissues of cancer patients. Therefore, a specific tumor marker has a good application prospect in clinical diagnosis [5].

The use of tumor markers in early breast cancer diagnosis can effectively improve the sensitivity and specificity, and contribute to early disease

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diagnosis. E-cadherin, a member of the cadherin family, is a calcium-dependent transmembrane glycoprotein, mainly expressed in epithelial cells. It is encoded by the cadherin-1 (CDH1) gene on chromosome 16q22.1, with a molecular weight of approximately 120000 [6]. E-cadherin mediates the adhesion of allogeneic epithelial cells, plays an important role in epithelial cell aggregation and adhesion and in maintaining the integrity of epithelial morphology and structure, and is the most important molecule mediating epithelial cell adhesion [7]. Studies have shown that the expression of E-cadherin is closely related to the invasion and metastasis of breast cancer, and can be used as an index for the evaluation of breast cancer [8]. It has been shown that GATA-3 plays an extremely important role in the development and progression of breast cancer and can reverse the epithelial-mesenchymal transition (EMT) through several mechanisms to inhibit the metastasis of breast cancer [9]. It regulates the proliferation, differentiation and development of cells mainly by binding to the [(A /T) GATA (A /G)] sequence of DNA [10]. Several authors [11] have shown that GATA-3 expression is closely related to breast cancer and can be used as a biomarker for this disease.

In this paper, the expression levels of transcription factors GATA3 and E-cadherin in breast cancer tissues were detected by real-time quantitative PCR (RT-PCR), and the value of GATA3, E-cadherin single diagnosis and combined diagnosis of breast cancer was compared to explore the effect of GATA3 combined with E-cadherin in the diagnosis and treatment of breast cancer and to evaluate its clinical value.

Methods

General information

120 breast cancer patients in Affiliated Tumor Hospital of Guangxi Medical University from May 2014 to December 2016 were selected as the experimental group. All patients were female with age range 32-70 years (mean 58.7) and with pathologically confirmed breast cancer. According to the clinical staging, there were 47 cases in stage I-II and 73 cases in stage III-IV. There were 53 cases with lymph node metastasis and 67 cases without. At the same time, 80 healthy women with age range 35-65 years (mean 57.2) were selected as the control group.

Inclusion criteria

Patients with complete clinicopathological data. Patients without neoadjuvant chemotherapy, radiation therapy or endocrine therapy. Patients with assessment of liver and kidney function, breast and axillary lymph node B ultrasound, tumor markers, blood routine tests, emission computed tomography (ECT), and assessment of the extent of the lesion and clinical staging within two weeks before surgery.

Exclusion criteria

Patients who refused or were unable for operation. Patients with other malignant tumors. Patients with reduced liver function and severe organ diseases. Patients with autoimmune system defects. Pregnant or lactating women. Patients who did not receive standard adjuvant therapy after surgery.

This study was approved by the ethics committee of our institute and the participants signed informed consent.

Detection methods

Three ml venous blood of patients in the experimental and the control group were collected on an empty

Table 1. Comparison of baseline data between the experimental group and the control group [n/(%)]/(x±s)

Indicators	*Experimental group (n=120)*	*Control group (n=80)*	x^2/t	*p*
Age, years (mean±SD)	60.89±9.13	58.87±8.97	-1.392	0.308
BMI (kg/m2) (mean±SD)	19.62±3.09	19.84±2.87	3.304	0.15
History of smoking, n (%)			0.051	0.822
Yes	21(15)	15(18.75)		
No	99(82.5)	65(81.25)		
History of hypertension, n (%)			0.139	0.709
Yes	39(32.5)	24(30)		
No	81(67.5)	56(70)		
HB(gm/dl), mean±SD	11.51±1.74	12.01±2.31	1.322	9.44
PLT($\times10^9$/L), mean±SD	152.76±21.79	157.12±22.56	0.968	0.536
WBC($\times10^9$/L), mean±SD	7.41±2.53	7.12±2.29	-1.411	0.875
RBC($\times10^{12}$/L), mean±SD	4.39±0.54	4.21±0.49	-3.583	0.808
ALT(U/L), mean±SD	22.76±10.01	21.12±9.95	-5.660	0.274
AST(U/L), mean±SD	19.67±7.89	18.21±6.98	-1.261	0.433

stomach in the morning, placed in anticoagulant tubes and sent to the laboratory. The venous blood sample was centrifuged at 3000 r/min for 10 min, and the serum was separated and stored in a freezer at -20°C for later use, avoiding repeated freezing and thawing. GATA3 and E-cadherin kits were purchased from Shanghai TW Reagent Industrial Co., Ltd., and the models were TWp009009 and TWp028616, respectively. The instrument was BS-1101 enzyme label analyzer from Beijing Linmao Technology Co., Ltd.

Operational steps

(1) GATA3 and E-cadherin kits for ELISA were placed at room temperature for 20 min. (2) 50 µl standard solution were added to 96-well plates after being diluted 5 times and the blank well was made at the same time (Steps in the blank control well was the same as in other steps, but without enzyme labeled reagent and samples). When adding the sample to the bottom of the well of the enzyme-labeled plate, it was not allowed to touch the wall of the well. The reaction wells were sealed with a sealing film and then incubated in a 37°C water bath or incubator for 30 min. (3) After uncovering the sealing film, the samples were discarded and dried with absorbent paper, and each reaction well was filled with phosphate buffered saline (PBS). After standing for 30 s, this step was repeated five times and the well was dried. (4) Exempting the blank wells, 50 µl of the enzyme labeled reagent were added to each well and incubated at 37°C for 30 min, while the washing was the same as in step 3. (5) 50 µl of each substrate A, B were added to each well, and incubated at 37°C for 30 min in the dark. (6) 50 µl citric acid termination solution were added to each well, and the wells were zeroed with blank well, while the absorbance value (OD value) of each well was measured at a wavelength of 450nm in 25 min. And the expression levels of GATA3 and E-cadherin were calculated.

Observation indicators

(1) The expression levels of GATA3 and E-cadherin in the experimental group and the control group were detected and compared. (2) The expression levels of GATA3 and E-cadherin before and after surgery were measured.

Statistics

SPSS 17.0 statistical software (Shanghai Yuchuang Network Technology Co., Ltd.) was used to analyze the relevant data, which were presented as by mean±standard deviation (x±s). T-test was used for comparison between the two groups; Receiver operating characteristics (ROC) was used to evaluate the sensitivity and specificity of

Table 2. Correlation between GATA3, E-cadherin and clinicopathological characteristics

Clinicopathological characteristics	*Cases*	*GATA3 (ng/ml)*	*t*	*p*	*E-cadherin (ng/ml)*	*t*	*p*
Age, years			-0.634	0.305		2.614	0.289
≤50	48	13.32±3.49			3.35±1.98		
>50	72	13.98±4.21			3.01±1.52		
Lymph node metastasis			-0.058	0.789		-1.175	0.209
Yes	53	13.14±3.67			2.62±1.76		
No	67	12.78±3.12			3.25±1.89		
Tumor diameter, cm			-4.016	0.492		2.427	0.059
≤2	38	11.12±3.87			3.31±1.87		
>2	82	13.21±3.32			2.78±1.69		
Vessel invasion			3.879	0.440		-3.807	0.093
Yes	41	13.79±4.15			2.51±1.73		
No	79	12.61±3.76			3.51±1.86		
Clinical stage			-6.335	<0.05		9.415	<0.05
I-II	47	10.12±2.14			4.67±1.87		
III-IV	73	13.98±4.11*			2.54±1.32*		
HER-2			4.576	<0.05		-6.94	<0.05
+	69	13.64±3.78			2.32±1.17		
-	51	11.02±2.17*			3.87±1.96*		
ER			-4.680	<0.05		3.843	<0.05
+	57	10.97±2.73			3.69±1.91		
-	63	13.89±3.88*			2.52±1.31*		
PR			-3.699	<0.05		1.700	<0.05
+	52	11.23±2.32			3.68±1.87		
-	68	13.87±3.69*			2.63±1.32*		

*There was a significant difference in the comparison between different clinical stages, HER2, ER and PR (p<0.01)

single and combined detection. Binary logistic regression analysis was used to analyze the diagnostic value of combined detection of GATA3 and E-cadherin in breast cancer. A p value <0.05 was considered statistically significant.

Results

Comparison of baseline data between the experimental group and the control group

There was no difference in the general clinical baseline data such as age, body mass index (BMI), history of smoking and hypertension, hemoglobin (Hb), platelet (PLT) count, white blood cell (WBC) count, red blood cell (RBC) count, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) between the experimental group and the control group (p>0.05) (Table 1).

Correlation between GATA3, E-cadherin and clinicopathological characteristics

Through data compilation, it was concluded that the expression level of GATA3 in breast cancer patients was not significantly correlated with age, lymph node metastasis, tumor diameter, or vessel invasion (p>0.05), but it was correlated with clinical stage, HER-2, estrogen (ER) and progesterone receptor (PR) (p<0.05). The expression level of E-cadherin was not significantly correlated with age, lymph node metastasis, tumor diameter, or vessel invasion (p>0.05), but it was correlated with clinical stage, HER-2, ER and PR (p<0.05) (Table 2).

Comparison of the expression levels of GATA3 and E-cadherin between the two groups

The expression levels of GATA3 and E-cadherin in the experimental group and the control group were detected. Table 3 shows that the mean expression of GATA3 in the experimental group was 13.96 ± 4.13 ng/ml, and the expression level in the control group was 7.89 ± 3.08 ng/ml. The expression level of GATA3 in the experimental group was significantly higher than that in the control group (p<0.01). Table 3 also shows that the mean expression of E-cadherin in the experimental group was 3.34 ± 1.96 ng/ml, and the expression in the control group was 7.98 ± 2.85 ng/ml. The expression level of E-cadherin in the experimental group was significantly lower than that in the control group (p<0.01) (Table 3).

Comparison of the value of GATA3 and E-cadherin single detection and combined detection in the diagnosis of breast cancer

The sensitivity was 90.0% (combined detection), 82.5% (GATA3) and 82.5% (E-cadherin). The specificity was 91.67% (combined detection), 87.50% (E-cadherin) and 73.33% (GATA3). The results showed that the sensitivity and specificity of serum GATA3 combined with E-cadherin were the highest. The Youden index of GATA3 single detection for breast cancer was 0.61, for E-cadherin single detection it was 0.70 and for the combined detection it was 0.82. For breast cancer screening, the higher the Youden index, the better the detection effect and the higher the authenticity (Table 4).

In healthy women the ROC curve plotted according to the sensitivity and specificity of single

Table 3. Comparison of the expression levels of GATA3 and E-cadherin between the two groups

Groups	*Cases (n)*	*GATA3 (ng/ml) mean±SD*	*E-cadherin (ng/ml) mean±SD*
Experimental group	120	13.96±4.13*	3.34±1.96*
Control group	80	7.89±3.08	7.98±2.85
t		10.13	-14.2
p		<0.01	<0.01

*Compared with the expression level in the control group, p<0.01

Table 4. Comparison of the value of GATA3 and E-cadherin single detection and combined detection in the diagnosis of breast cancer

Indicators	*Sensitivity (%)*	*Specificity (%)*	*Youden index*
GATA3	87.5	73.3	0.61
E-cadherin	82.5	87.5	0.70
GATA3+E-cadherin	90.0	91.7	0.82

Table 5. Evaluation of the value of GATA3 and E-cadherin single detection and two combined detection in the diagnosis of breast cancer

Detection method	*The best cut-off value*	*AUC*	*Standard error*	*p*	*95% CI*	
					Upper limit	*Lower limit*
GATA3	10.96	0.8519	0.534	<0.01	0.7790	0.9047
E-cadherin	5.64	0.9144	0.329	<0.01	0.8719	0.9569
GATA3+E-cadherin	-	0.9588	0.032	<0.01	0.9314	0.9861

CI: confidence interval

detection and combined detection revealed that the larger the area under curve (AUC), the greater the diagnostic value. The AUC of combined diagnosis was larger than that of single diagnosis. The best cut-off values of GATA3 and E-cadherin were 10.96 and 5.64, respectively, and the diagnostic efficiency was the highest at this point (Table 5 and Figure 1).

Levels of GATA3 and E-cadherin before and after surgery

The mean expression level of GATA3 in breast cancer patients before surgery was high (13.96±4.13 ng/ml). The mean expression level of GATA3 in breast cancer patients after surgery was 8.32±3.56 ng/ml. The difference between before and after surgery was significant (p<0.01). The mean expression level of E-cadherin in breast cancer patients before surgery was low (3.34±1.96 ng/ml). The mean expression level of E-cadherin in breast cancer patients after surgery was high (6.97±2.43 ng/ml), and the difference between before and after surgery was significant (p<0.01) (Table 6).

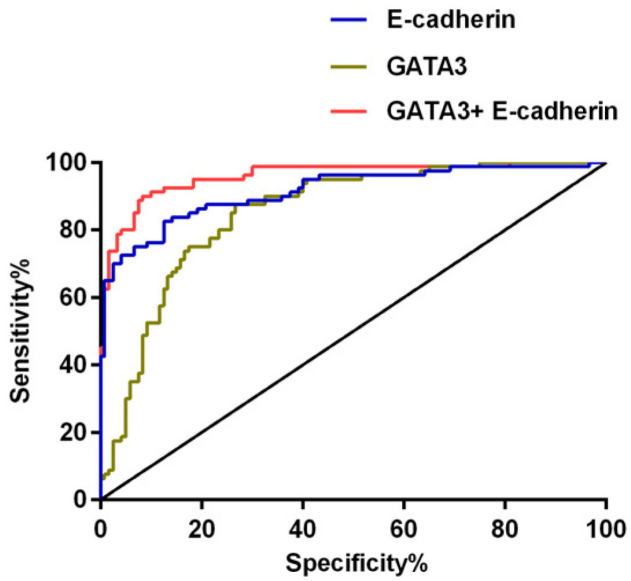

Figure 1. ROC curve of GATA3, E-cadherin single detection and combined detection in the diagnosis of breast cancer. The sensitivity and specificity of serum GATA3 combined with E-cadherin were the highest. The area under the curve (AUC) of the GATA3 and E-cadherin combined detection was larger than that of the single detection, and the diagnostic value was higher. The ROC curve of the combined detection was closer to the upper left corner than the single detection, and the detection accuracy was higher than the single detection.

Table 6. Changes of GATA3 and E-cadherin levels before and after surgery

	Cases	*GATA3 (ng/ml) mean±SD*	*E-cadherin (ng/ml) mean±SD*
Before surgery	120	13.96±4.13*	3.34±1.96*
After surgery	120	8.32±3.56	6.97±2.43
t		10.43	-13.37
p		<0.01	<0.01

Discussion

As a malignant tumor, breast cancer often occurs in the mammary epithelium tissues [12]. Related statistics have shown that breast cancer accounts for about 15% of the incidence of malignant tumors in women [13]. According to the 2015 WHO report, there has been a significant increase in the mortality rate of breast cancer among women, mainly due to recurrence and metastasis [14] and the unclear pathogenesis. Therefore, accurate diagnosis of breast cancer can improve the survival rate and cure rate of breast cancer patients [15]. Due to the low sensitivity of single detection of tumor markers, the combined detection of various tumor markers has been used, which can improve the accuracy of tumor diagnosis and has a certain clinical value [16]. Studies have shown that GATA3 is closely related to breast cancer tissues [17], and its expression rate in breast cancer is 47-100% [18-20]. Related studies have shown that the expression of E-cadherin gene is closely related to the invasion of breast cancer, and has a certain significance for the diagnosis of breast cancer [8].

In this study, the results of Table 2 showed that the expression levels of GATA3 and E-cadherin in breast cancer patients were correlated with clinical stage, HER-2, ER and PR (p<0.05), which were consistent with the results of Kouros-Mehr et al. study [21]. Abba et al. [22] have found that the expression of GATA3 is closely related to the state of ER/PR, and was related to the histological grade of breast cancer. Theodorou et al. [23] have confirmed that GATA3, as a key molecule in the estrogen receptor (ESR1) complex, contributes to recurrence and metastasis by participating in the function of ER signaling pathway. ER is also a target of endocrine therapy for breast cancer and a good prognostic marker. There is a positive correlation between the expression of E-cadherin and the expression of ER, which indicates the expression of E-cadherin is related to the involvement of ER in clinicopathology, but further research is still needed [24]. High expression of GATA-3 in breast cancer patients is a very important feature of Luminal type breast cancer, and is associated with better prognosis [25]. Studies have shown that GATA3 in breast cancer forms GATA-3/G9A/ NuRD complex to inhibit one of the key genes of EMT (ZEB2), and finally to inhibit the development of

distant metastasis of breast cancer [26]. The expression level of E-cadherin in the experimental group was significantly lower than that in the normal control group ($p<0.01$), indicating that the expression level of E-cadherin was negatively correlated with breast cancer, which was consistent with the results of Weissenbacher et al. study [27]. Low expression of E-cadherin in breast cancer is related to the methylation degree of its own promoter, which inhibits the expression of epithelial-derived genes and speeds up the progression and metastasis of breast cancer [28]. GATA3 is highly expressed in breast cancer and lowly expressed in normal breast tissue [20]. As a tumor suppressor, the expression of E-cadherin has a high inhibitory effect on tumor progression, invasion and metastasis. It is highly expressed in normal breast tissues and down-regulated in normal breast tissues [29]. Park et al. [30] and other researchers believe that E-cadherin can be used as an effective index for screening high risk groups for recurrence and metastasis after surgery. Gauger et al. [31] put forward the concept of epidermal-mesenchymal transition (EMT), which suggests that epithelial cells are transformed to interstitial cells under certain physiological or pathological conditions, thus having the ability to move. EMT can be reversed through a variety of mechanisms, thereby inhibiting the metastasis of breast cancer [8]. E-cadherin is considered to be a tumor suppressor, which plays an important role in maintaining the morphology of epithelial cells and intercellular recognition [32].

In conclusion, the expression levels of GATA3 and E-cadherin have certain clinical value for early diagnosis of breast cancer. Moreover, the combined diagnosis of GATA3 and E-cadherin is more valuable than the single detection, has a better diagnostic value and it is expected to become an effective indicator for the diagnosis of breast cancer in the future.

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Conflict of interests

The authors declare no conflict of interests.

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