Original Article

Association of high insulin receptor expression with poor prognosis in patients with breast cancer

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Background: The aim of this study was to investigate the expression of insulin receptor (IR) in the blood vessels of patients with breast cancer (BC) with or without type 2 diabetes mellitus (DM2) and its relationship with histopathological features of BC tissues and patient prognosis.

Methods: A total of 124 patients with BC diagnosed and treated at The Affiliated Hospital of Putian University between January 2018 and January 2019 were eligible for this study. According to the presence or absence of DM2, they were then divided into 2 groups: patients with BC and DM2 (DBC group, n=26) and patients with BC and without DM2 (BC group, n=98). The expression of IR in the cancer and adjacent tissues was detected using immunohistochemistry. The patients were followed up for 1 year. Kaplan-Meier analysis was used to compute the overall survival (OS) of the patients with BC. Furthermore, Cox regression was employed to investigate the correlation of IR expression with DM2, pathological tissue, TNM stage, and OS.

Results: IR expression in cancer tissues (34.7%) was significantly higher than that in adjacent normal tissues (15.3%). Among cancer tissues, IR was highly expressed in DBC tissues (57.7%) compared with BC tissues (28.6%). IR was also highly expressed in patients with tumor infiltration and lymphatic metastasis. Its expression was significantly correlated with T stage and N stage, but not with M stage. In addition, patients with high IR expression had significantly lower survival than did those with low IR expression. Moreover, univariate and multivariate Cox regression analysis indicated that tumor infiltration, lymphatic metastasis, tumor size, T stage, and high IR expression were independent risk factors for BC prognosis.

Conclusions: High IR expression was associated with poor prognosis of patients with BC. The expression of IR may be a promising indicator to assess the survival of patients with BC.

Keywords: Breast cancer; insulin receptor; diabetes mellitus; prognosis

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Introduction

Breast cancer (BC) is the most common cancer and the fifth leading cause of cancer death worldwide. According to statistics, there were 2.3 million new cases of BC in 2020, accounting for 11.7% of the total number of new cancer cases, and this number is expected to reach 4.4 million by 2070 (1-3). Additionally, epidemiological data has shown that BC has the highest incidence among malignant tumors in female patients, accounting for about 24.5%, and the incidence has increased worldwide in recent years (1). The data from National Central Cancer Registry of China (NCCR) indicates that the incidence and mortality of BC in Chinese women gradually increased from 1973 to 2015, with approximately 420,000 new BC cases in 2020 (3,4).

With the progress of screening and treatment, the mortality rate of BC is decreasing year by year, but tumor invasion, metastasis, and recurrence are still important causes for death in patients with BC. Therefore, it is important to find reliable prognostic indicators for the monitoring and treatment of BC.

In recent years, many studies have linked diabetes to the risk for cancers, and a growing body of evidence suggests that diabetes, especially type 2 diabetes mellitus (DM2), is an independent risk factor for site-specific cancer and patient prognosis (5). Several epidemiological studies also found that patients with diabetes have an increased risk of different types of cancer, such as breast, pancreatic, liver, and colorectal cancers (6-9). Up to 15% of patients with BC have DM2, which raises the risk of recurrence, distant metastasis, and mortality of these patients (9). The overall survival rate of patients with BC and DM2 (DBC) is significantly worse than that of patients without DM2 (10). These results indicate an association of DM2 with BC progression. A study has also found that patients with DBC have a higher pathological stage and more aggressive histological grade. Additionally, DM2 has been associated with insulin resistance and systemic inflammation, which can induce hyperglycemia and dyslipidemia, alter circulating amino acids, and increase the availability of glucose, fatty acids, and glutamine for BC cells. Thus, systemic and cellular metabolism provides a favorable metabolic environment and pathogenic stimuli for the occurrence and development of BC (11).

DM2 is closely related to insulin resistance caused by diminished insulin receptor (IR) signaling or insulin insensitivity. IR belongs to subclass II of the tyrosine kinase receptor superfamily, with two isoforms, IR-A and IR-B, and has a critical role in regulating glucose metabolism, lipids, and proteins in the target tissues of insulin, such as liver, muscle, and adipose tissue (12). A study showed that IRS is the substrate of activated insulin receptor tyrosine kinase, with many residues, phosphorylated, phosphorylated proteins involved in cytokine signal transduction, control the downstream signal transduction, participate in cell proliferation, differentiation, apoptosis and immune regulation, and other functions. When it is abnormal, it can make cells cancerous and lead to tumor (13). Among its isoforms, IR-A is a dual receptor for insulin and insulin-like growth factor (IGF)-II, which is highly expressed in most malignancies. The overexpression of IR-A in cancer cells can mediate the effects of locally produced autocrine and/or paracrine IGF-II and the effects of circulating insulin, ultimately stimulating tumor progression (14,15). A study has shown that IR-A overexpression is associated with increased cancer risk and poor prognosis of patients with DBC (16). In addition, overexpression of IR in the vascular endothelium of various malignancies has been found to be associated with a relative increase in IR-A expression (17). However, more research is needed to investigate whether diabetes affects IR expression in tumor tissue and blood vessels in the tissues of patients with BC and to confirm the relationship between IR expression and the clinicopathological features and prognosis of BC.

This study thus aimed to analyze this unconfirmed relationship based on immunohistochemistry results of IR expression in the blood vessels of cancer and normal adjacent tissues of BC patients with or without DM2. We present the following article in accordance with the REMARK reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-13/rc).

Highlight box

Key findings

- High insulin receptor (IR) expression was associated with the poor prognosis of patients with breast cancer (BC).

What is known and what is new?

- Type 2 diabetes mellitus and insulin therapy may be independently associated with poor prognosis in BC.
- IR expression in tumor tissues of patients with BC was associated with risk factors such as tumor infiltration, lymphatic metastasis, T stage, and N stage. High IR expression was associated with poor prognosis of patients with BC.

What is the implication, and what should change now?

- IR may be a promising marker for estimating the prognosis of patients with BC and might be used to guide the clinical management and treatment of these patients.

Methods

Study participants

A total of 124 patients diagnosed with BC in the Affiliated Hospital of Putian University between January 2018 and January 2019 were eligible for this study based on the following inclusion criteria: (I) they met the diagnostic criteria for BC, (II) they were not treated with radiotherapy or chemotherapy, (III) they had no metabolic disease except diabetes, and (IV) the patients or their families provided

signed informed consent. The exclusion criteria were the following: (I) BC combined with hyperplasia of mammary glands and other diseases, (II) a history of BC-related surgery, (III) pregnant or lactating, and (IV) combined with traumatic infection. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The Affiliated Hospital of Putian University (No. 202201056) and informed consent was taken from all the patients.

Patients with BC were divided into a DBC group (patients with BC and DM2, n=26) and a BC group (patients with BC and without DM2, n=98) according to the following diagnostic criteria for diabetes established by the International Diabetes Federation (18): fasting blood glucose ≥7.0 mmol/L and/or 2-h postprandial glucose ≥11.1 mmol/L. Cancer and normal adjacent tissues of the DBC and BC groups were collected. The general data of the patients were recorded. All the included patients were followed up for 1 year after treatment to record their survival status (death or survival).

The pathological subtypes were divided into 4 categories according to the biological and pathological characteristics of patients with BC (19): (I) luminal A—good prognosis, with a low diffusion rate, low grade, and low risk, along with tubular, cribriform, and classical lobular tissue; (II) luminal B—moderate prognosis, with micropapillary and pleomorphic lobular tissue; (III) human epidermal growth factor receptor (HER-2) positive—a prognosis considered second to luminal B subtype, with observable invasive tissue; (IV) triple-negative BC (TNBC)—poor prognosis, with special pathological tissue structure mainly manifesting as medullary carcinogenesis and adenoid cystic BC. The histological grade and TNM stage of BC were determined according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual Eighth Edition (20). Specifically, histological grade was divided into well, moderately, or poorly differentiated according to the degree of differentiation. The TNM stage of BC was then simplified to T stage (T1, T2, T3, and T4), N stage (N0, N1, N2, and N3), and M stage (M0 and M1).

Immunohistochemistry

Paraffin-embedded tumor tissues were sectioned, routinely deparaffinized using xylene and ethanol, and then rehydrated. Subsequently, 30% hydrogen peroxide was used to block endogenous peroxidase activity, which was followed by application of citrate buffer for antigen retrieval. IR antibody (1:100; ab60946; Abcam) was added and incubated overnight at 4 ℃. Diaminobenzidine (DAB) was used for visualization after secondary antibody incubation. The sections were then stained with hematoxylin and dehydrated with ethanol, which was followed by washing and mounting with coverslips. The IR expression was evaluated with a semiquantitative method. The staining result was scored using a combination of the staining intensity and the percentage of stained vessels. (I) Staining intensity was scored as follows: 0 points, no staining; 1 point, light yellow; 2 points, light brown; and 3 points, dark brown. (II) The percentage of stained vessels was scored as follows: 0 points, no staining; 1 point, 1% to 25% of stained vessels; 2 points, 26% to 50% of stained vessels; 3 points, 51% to 75% of stained vessels; and 4 points for 76% to 100% of stained vessels. The final result was obtained by adding the 2 scores, with 0–2 points referring to no expression, 3–5 points referring to low expression, and ≥6 points referring to high expression. Immunohistochemical scoring was performed by 2 pathologists who were blinded to the study. The disagreements between the 2 were resolved in consultation with a third investigator.

Statistical analysis

SPSS 22.0 software (IBM Corp.) was used for statistical analyses of the obtained data. Measurement data are expressed as the mean ± standard deviation (SD), and the *t*-test was used to compare data between 2 groups. Enumeration data are expressed as numbers and percentages, and the chi-squared test was used for comparison. The Kaplan-Meier method and log-rank test were employed to analyze the overall survival (OS) of patients with BC, and Cox regression was used to determine the effects of each clinicopathological feature on the OS. $P<0.05$ was used to indicate a statistically significant difference.

Results

General patient information

Of the 124 eligible cases, there were 9 males and 115 females, aged 28–83 years. There were no significant differences between the DBC and BC groups in age, body mass index, biochemical parameters, pathological classification, or tumor infiltration. However, a significant difference was identified in low-density lipoprotein levels between the 2 groups (*Table 1*).

Table 1 General patient information

Item	DBC (n=26)	BC (n=98)	P
Gender			0.467[a]
Male	0 (0.0)	9 (9.2)	
Female	26 (100.0)	89 (90.1)	
Age (years)	52.54±8.77	50.78±12.11	0.489[b]
BMI (kg/m^2)	24.85±3.86	24.05±3.77	0.340[b]
Systolic blood pressure (mmHg)	128.73±23.51	124.14±13.97	0.207[b]
Diastolic blood pressure (mmHg)	81.35±10.28	78.23±10.86	0.192[b]
Triglyceride	0.93±0.21	0.99±0.18	0.086[b]
Cholesterol	4.45±0.46	4.37±0.46	0.479[b]
Low-density lipoprotein	2.37±0.53	2.59±0.45	0.039*[b]
High-density lipoprotein	1.34±0.21	1.34±0.19	0.953[b]
Apolipoprotein	1.73±0.34	1.65±0.25	0.187[b]
Histological grade			0.090[a]
Well differentiated	2 (7.7)	18 (18.4)	
Moderately differentiated	15 (57.7)	52 (53.1)	
Poorly differentiated	9 (34.6)	28 (28.6)	
Pathological classification			0.668[a]
Luminal A	8 (30.8)	32 (32.7)	
Luminal B	11 (42.3)	38 (38.8)	
HER-2 positive	4 (15.4)	9 (9.2)	
TNBC	3 (11.5)	19 (19.4)	
Tumor infiltration			0.054[a]
Noninfiltrating	7 (26.9)	47 (48.0)	
Infiltrating	19 (73.1)	51 (52.0)	
Lymphatic metastasis			0.330[a]
Nonmetastatic	15 (57.7)	46 (46.9)	
Metastatic	11 (42.3)	52 (53.1)	
Menopause			0.268[a]
No	12 (46.2)	52 (53.1)	
Yes	14 (53.8)	37 (46.9)	
Tumor size			0.255[a]
<3 cm	19 (73.1)	71 (72.4)	
≥3 cm	7 (26.9)	27 (27.6)	
T stage			0.089[a]
T1	8 (30.8)	34 (34.7)	
T2	16 (61.5)	42 (42.9)	
T3	0 (0.0)	16 (16.3)	
T4	1 (3.8)	6 (6.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Item	DBC (n=26)	BC (n=98)	P
N stage			0.085[a]
N0	11 (42.3)	44 (44.9)	
N1	8 (30.8)	32 (32.7)	
N2	3 (11.5)	17 (17.3)	
N3	4 (15.4)	5 (5.1)	
M stage			0.515[a]
M0	26 (100.0)	93 (94.9)	
M1	0 (0.0)	5 (5.1)	
History of drug use			0.234[a]
No	9 (34.6)	28 (28.6)	
Yes	17 (65.4)	70 (71.4)	
History of diseases			0.742[a]
No	15 (57.7)	53 (54.1)	
Yes	11 (42.3)	45 (45.9)	

Data are expressed as mean ± SD or n (%). *, P<0.05 *vs.* BC group; [a], Chi-squared test; [b], *t*-test. DBC, diabetic breast cancer; BC, breast cancer; BMI, body mass index; HER-2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Table 2 Comparison of insulin receptor expression between breast cancer patients with diabetes and without diabetes

Group	Case (n)	Low IR expression, n (%)	High IR expression, n (%)	χ^2	P
DBC	26	11 (42.3)	15 (57.7)	7.693	0.006**
BC	98	70 (71.4)	28 (28.6)		

**, P<0.01 *vs.* BC group. DBC group, diabetic breast cancer with type 2 diabetes mellitus; BC group, breast cancer without type 2 diabetes mellitus; IR, insulin receptor.

Table 3 Comparison of insulin receptor expression between breast cancer tissue and adjacent tissue

IR expression	Low IR expression, n (%)	High IR expression, n (%)	χ^2	P
Cancer tissue (n=124)	81 (65.3)	43 (34.7)	22.042	≤0.001***
Adjacent tissue (n=124)	105 (84.7)	19 (15.3)		

***, P<0.001 *vs.* adjacent tissue. IR, insulin receptor.

IR was highly expressed in BC tissues, especially in those with diabetes

To clarify the relationship between IR expression and diabetes, we analyzed the expression of IR in tissues. We found that IR expression was significantly higher in the DBC group (57.7%) than in the BC group (28.6%) (*Table 2*), indicating a higher detection rate of high IR expression in tumor-related vessels in patients with DBC. We also detected the IR expression in cancer tissues and adjacent noncancerous tissues, and the results showed that the expression of IR was significantly higher in BC tissues (34.7%) than in normal adjacent tissues (15.3%) (*Table 3*).

High expression of IR was associated with the histopathological features of BC

The relationship between IR expression and the

clinicopathological characteristics of patients with BC was further analyzed. As shown in *Table 4*, IR expression in BC tissues with/without diabetes was not associated with gender, age, body mass index, triglyceride, cholesterol, low-density lipoprotein, high-density lipoprotein, apolipoprotein, menopausal status, pathological subtype, histological grade, tumor size, history of drug use, or history of diseases. No significant difference was identified in the presence or absence of tumor infiltration or lymphatic metastasis in patients with low IR expression; the proportion of high IR expression in patients with tumor infiltration and lymphatic metastasis was significantly higher than in patients with noninfiltrating and nonmetastatic tumors. In addition, IR expression was also significantly correlated with T stage and N stage ($P<0.05$) but not with M stage ($P>0.05$).

Univariate and multivariate Cox regression analyses were

Table 4 Relationship between insulin receptor expression and each clinicopathological characteristic

Variables	Low IR expression (n=81)	High IR expression (n=43)	t/χ^2	P
Gender			1.867	0.172[a]
Male	4 (4.9)	5 (11.6)		
Female	77 (95.1)	38 (88.4)		
Age (years)	50.01±11.49	53.28±11.29	1.516	0.132[b]
BMI (kg/m^2)	24.06±3.40	24.53±4.46	0.669	0.505[b]
Systolic blood pressure (mmHg)	123.84±16.89	127.49±15.43	1.179	0.241[b]
Diastolic blood pressure (mmHg)	78.67±10.84	79.30±10.77	0.311	0.756[b]
Triglyceride	0.99±0.18	0.96±0.20	0.772	0.442[b]
Cholesterol	4.38±0.44	4.40±0.50	0.171	0.864[b]
Low-density lipoprotein	2.57±0.44	2.49±0.54	0.921	0.359[b]
High-density lipoprotein	1.33±0.20	1.36±0.17	0.863	0.39[b]
Apolipoprotein	1.68±0.26	1.62±0.29	1.098	0.274[b]
Histological grade			3.104	0.212[a]
Well differentiated	16 (19.8)	4 (9.3)		
Moderately differentiated	44 (54.3)	23 (53.5)		
Poorly differentiated	21 (25.9)	16 (37.2)		
Pathological classification			1.151	0.765[a]
Luminal A	26 (32.1)	14 (32.6)		
Luminal B	32 (39.5)	17 (39.5)		
HER-2 positive	10 (12.3)	3 (7.0)		
TNBC	13 (16.0)	9 (20.9)		
Tumor infiltration			6.551	0.010[a]
Noninfiltrating	42 (51.9)	12 (27.9)		
Infiltrating	39 (48.1)	31 (72.1)		
Lymphatic metastasis			7.289	0.007[a]
Nonmetastatic	47 (58.0)	14 (32.6)		
Metastatic	34 (42.0)	29 (67.4)		

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Low IR expression (n=81)	High IR expression (n=43)	t/χ^2	P
Menopause			1.454	0.228[a]
No	45 (55.6)	19 (44.2)		
Yes	36 (44.4)	24 (55.8)		
Tumor size			0.112	0.738[a]
<3 cm	58 (71.6)	32 (74.4)		
≥3 cm	23 (28.4)	11 (25.6)		
T stage			13.491	0.004[a]
T1	30 (37.0)	12 (27.9)		
T2	42 (51.9)	16 (37.2)		
T3	8 (9.9)	8 (18.6)		
T4	1 (1.2)	7 (16.3)		
N stage			14.373	0.002[a]
N0	42 (51.9)	13 (30.2)		
N1	28 (34.6)	12 (27.9)		
N2	9 (11.1)	11 (25.6)		
N3	2 (2.5)	7 (16.3)		
M stage			0.540	0.462[a]
M0	79 (97.5)	40 (93.0)		
M1	2 (2.5)	3 (7.0)		
History of drug use			2.495	0.114[a]
No	28 (34.6)	9 (20.9)		
Yes	53 (65.4)	34 (79.1)		
History of diseases			0.048	0.826[a]
No	45 (55.6)	23 (53.5)		
Yes	36 (44.4)	20 (46.5)		

Data are expressed as mean ± SD or n (%). [a], Chi-squared test; [b], *t*-test. IR, insulin receptor; BMI, body mass index; HER-2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

performed to evaluate the relationship between high IR expression in tumor-related vessels and the occurrence and development of BC. The variables with statistical significance obtained in univariate Cox regression analysis were then included in multivariate Cox regression analysis. The results showed that tumor infiltration (P=0.041), lymphatic metastasis (P=0.033), tumor size (P=0.013), T stage (P=0.030), and IR (P=0.042) were independent risk factors affecting the OS of BC (*Table 5*) and that patients with tumor invasion, lymphatic metastasis, larger tumor size, higher T stage, or high expression of IR had a shorter OS time.

High expression of insulin receptor was associated with poor prognosis in patients with BC

After the patients were followed up for 1 year, the deaths in the patient groups were recorded. The Kaplan-Meier survival curve showed that patients with BC with low IR expression had significantly longer OS than did those with high IR expression (*Figure 1*).

Table 5 Univariate and multivariate Cox regression analysis

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender	0.969 (0.127–7.382)	0.976		
Age	0.992 (0.948–1.037)	0.718		
BMI	0.962 (0.829–1.116)	0.605		
Systolic blood pressure	1.006 (0.977–1.036)	0.687		
Diastolic blood pressure	1.023 (0.977–1.070)	0.334		
Triglyceride	0.407 (0.024–6.888)	0.533		
Cholesterol	0.952 (0.318–2.852)	0.930		
Low-density lipoprotein	2.072 (0.697–6.157)	0.190		
High-density lipoprotein	0.213 (0.015–3.106)	0.258		
Apolipoprotein	0.891 (0.127–6.237)	0.908		
Histological grade	1.468 (0.661–3.259)	0.345		
Pathological classification				
Luminal A	1.000			
Luminal B	1.260 (0.355–4.471)	0.721		
HER-2 positive	0.707 (0.079–6.328)	0.756		
TNBC	1.974 (0.493–7.896)	0.336		
Tumor infiltration	3.75 (1.055–13.330)	0.041	4.283 (1.061–17.292)	0.041
Lymphatic metastasis	15.119 (1.987–115.055)	0.009	10.276 (1.214–87.005)	0.033
Menopausal status	0.701 (0.249–1.973)	0.501		
Tumor size	3.262 (1.182–9.003)	0.022	4.935 (1.391–17.507)	0.013
T stage	2.658 (1.581–4.467)	≤0.001	2.137 (1.076–4.246)	0.030
N stage	1.861 (1.164–2.976)	0.010	0.550 (0.259–1.172)	0.122
M stage	2.536 (0.330–19.524)	0.371		
History of drug use	2.675 (0.603–11.854)	0.195		
History of diseases	1.056 (0.383–2.913)	0.917		
Insulin receptor	4.762 (1.615–14.043)	0.005	3.677 (1.05–12.877)	0.042

BMI, body mass index; HER-2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; HR, hazard ratio; CI, confidence interval.

Discussion

BC has become the most common malignant tumor threatening women's health, and its incidence is increasing. Although current treatment options for BC, such as radiotherapy, chemotherapy, surgical treatment, endocrine therapy, and molecular targeted therapies, can prolong patient survival to some extent, the clinical efficacy and patients' prognosis and quality of life still need to be improved (21,22). Although the pathogenesis of BC has not been clarified, diabetes has been proven to be an independent risk factor for BC, which can affect the occurrence and development of BC through various biological mechanisms (23,24). Insulin often binds to IR in order to exert its biological function. The results of this

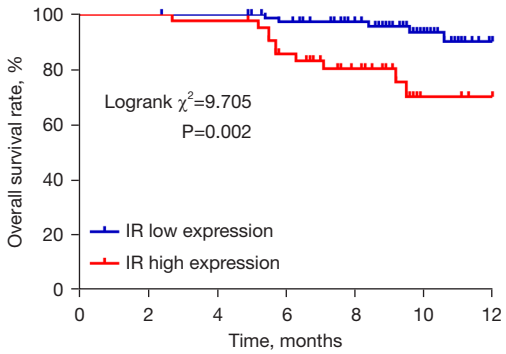

Figure 1 Kaplan-Meier survival curve of breast cancer patients with different insulin receptor expression. IR, insulin receptor.

study showed that IR expression was significantly higher in the tumor tissues of patients with DBC than in patients with BC.

Metabolic syndromes, including obesity, hypertension, dyslipidemia, and hyperglycemia, are related to insulin resistance and hyperinsulinemia and are hallmarks of DM and cancer, resulting in an increased risk of DM-associated cancer. IR is a tetrameric receptor consisting of extracellular α subunits and transmembrane β subunits and can regulate cell proliferation, division, migration, and apoptosis (25,26). Several studies have shown that the overexpression of IR is closely related to the occurrence and development of tumors in the breast, colon, cervix, and prostate (27-29), and the expression of IR has been shown to be upregulated in BC tissues (30). In our study, we found that the expression of IR was significantly higher in BC carcinoma than in adjacent tissues, which is consistent with previous studies.

Insulin is known to bind with high affinity to IR and IGF-1. IGF-1 has a high affinity to IR and is often combined with IR to form IGF-1/IR (31,32). It has been reported that IGF-1/IR is present in all BC subtypes and is related to poor survival (33). These hybrid heterodimeric receptors play a consequential role in receptor signaling in normal and abnormal tissues. It has been reported that the autophosphorylation of IR/IGF-1R hybrid receptors in response to insulin and IGF-1 results in increased cell proliferation, indicating that hybrid receptors may be the major mediators of IGF signaling in these cells (34,35). In our study, we found that the expression of IR in tumor tissues was higher in patients with DBC than in patients with BC. This may be related to IGF-1/IR, but this speculation should be verified in further experiments.

Some studies have indicated that DM2 and insulin therapy may be independently associated with poor prognosis in BC (36). It has also been reported that IR expression has good prognostic value in premenopausal patients with BC (37). In our study, we found that patients with low IR expression in BC tissues had higher survival than did those with high IR expression. Meanwhile, the survival time was shorter in patients with tumor infiltration, lymphatic metastasis, larger tumor size, or higher T stage. In addition, high IR expression was also significantly correlated with tumor infiltration, lymphatic metastasis, T stage, and N stage, but not with other factors such as M stage. This points to there being a close biological behavioral relationship between IR overexpression and BC. High IR expression may play a role in promoting tumor infiltration and lymphatic metastasis and in enhancing the proliferation and invasion of BC cells. More studies should be conducted to test these conclusions and further explore their implications.

This study has several limitations. First, this was a retrospective study, and the number of cases analyzed was limited, especially the number of patients with DBC. In addition, *in vitro* and *in vivo* studies and larger cohort multicenter studies are needed to further validate these findings and confirm the actual impact of IR in BC.

Conclusions

In summary, IR expression in tumor tissues of patients with BC was associated with certain risk factors, including tumor infiltration, lymphatic metastasis, T stage, and N stage. High IR expression was associated with poor prognosis in patients with BC. IR may be a promising marker for estimating the prognosis of patients with BC and might be used to guide the clinical management and treatment of these patients.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-13/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-13/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-13/coif). The authors have no conflicts of interest to declare.

Ethical Statement: 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 ethics board of The Affiliated Hospital of Putian University (No. 202201056) and informed consent was taken from all the patients.

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