RESEARCH COMMUNICATION

Clinical Features and Molecular Phenotypes of Breast Cancer in Patients with Type-2 Diabetes Mellitus

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Abstract

Objective: To investigate the clinical features, molecular phenotypes and clinical prognosis of breast cancer patients with type-2 diabetes mellitus, thereby providing a basis for individualized therapy of breast cancer. Methods: 105 breast cancer patients with type-2 diabetes mellitus (DM) presenting from January 2005 to December 2010 were enrolled in this study. 200 breast cancer non-diabetic patients in the same period were randomly selected as the control group. The clinical data of DM group and control group were retrospectively analyzed. The SPSS12.0 software was used for statistics and survival analysis. Results: The mean age of the patients in DM group were of 57.2±11.8 years, which was older compared with the control group. The percentage of postmenopausal patients was 71.4% and the ratio of grade II+III was 98.8%, which was higher than the control group. The neoadjuvant chemotherapy response rate of DM group was 67.5%, which was lower than control group. The patients in DM group had later clinical stage and more lymph metastasis. The proportion of advanced breast cancer was 68.57% and the ratio of lymph node metastasis was 66.01%. All the difference was significant (P<0.05). But there was no significant difference in tumor size and molecular phenotype between the diabetic group with breast cancer and the control group. Disease-free survival and overall survival rates of DM group were 80.2% and 84.2%, which were worse than those in the control group. All the difference was significant (P<0.05). After excluding the patients with other causes of death, results of overall survival still showed worse in DM group, but the difference was not statistically significant(P>0.05). Serum insulin at fasting and two hours postprandial were higher than normal value in DM group, but serum insulin levels in the control group changed in the normal range. Conclusion: There were older patients, with a higher proportion of high pathological grade, more lymph node metastasis, later clinical stages in the diabetic group with breast cancer. Breast cancer patients with type-2 diabetes mellitus were at risk of a poor prognosis. Hyperinsulinemia may be the real cause of poor prognosis in breast cancer patients with type-2 diabetes.

Key words: Diabetes mellitus - breast cancer - clinical features - molecular phenotype - hyperinsulinemia

Asian Pacific J Cancer Prev, **12**, 2183-2188

Introduction

In recently two decades, obese population has been rising obviously with the development of social economy and the change of people's diet and lifestyle habits. The incidence of type-2 diabetes and breast cancer increased obviously and it had become an important risk factor threatening women healthy. Lots of epidemiological studies have focused on the relationship of attack risk between diabetes mellitus and breast cancer. Most cohort studies and case-control studies showed that incidence of breast cancer in type-2 diabetes patients had increased by 18-20% and the diabetes mellitus was one of the high risk factors (Barone et al., 2008; Gouveri et al., 2011; Inoue et al., 2006; Lipscombe et al., 2006; Michels et al., 2003). Some large-scale clinical studies found that type-2 diabetes could enhance the fatality rate of Postmenopausal obese women with breast cancer (Tseng et al., 2009; Verlato et al., 2005). Meta-analysis indicated that type-2 diabetes is associated with an increased risk of breast cancer (Larsson et al., 2007; Wolf et al., 2005; Carey et al., 2006). After some studies were carried to discuss the clinical feature, it was presented that grade malignancy of breast cancer was higher and the number of lymph node metastasis is more, and a majority of this subgroup was negative ER/PR. However, some other reports did not support these points. There are still no

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reports about molecular subtype of breast cancer in patients with type-2 diabetes and the curative effects of primary chemotherapy on it. So in this study, 105 breast cancer patients with type-2 diabetes mellitus (DM) in the Third Hospital of Nanchang city from January 2005 to December 2010 were retrospective analyzed and clinical features, curative effects of primary chemotherapy and molecular phenotype were summarized. The results will be the basis for making a diagnosis and treatment for individuation.

Materials and Methods

Clinical data

A total of 2476 breast cancer patients in the Third Hospital of Nanchang city from January 2005 to December 2010 were enrolled into this study, in which 141 patients were carcinoma in situ and 17 patients did not undergo radical surgery. 105 breast cancer patients with type-2 diabetes mellitus (DM) were the study group. 200 breast cancer patients with non-diabetic patients in the same period were randomly selected as the control group. Clinical data of the DM group and control group were retrospectively analyzed. The study was conducted in accordance with the Declaration of Helsinki and approval by the Third Hospital of Nanchang city ethics committee. Informed written consent was obtained from all subjects.

Diagnostic criteria for DM

The diagnostic criteria for DM was as follows: (i) Physical examination, medication history and Blood glucose monitoring of DM patients (type-2 diabetes mellitus was accurately diagnosed) were carried by physician before operation; (ii) Fasting blood-glucose≥7.0 mmol/L (1999 WHO/ IDF diagnostic criteria proposed that symptoms + fasting plasma glucose ≥ 7.0 mmol/L, or random blood glucose ≥ 11.11 mmol/L)

Evaluation criterion for neoadjuvant chemotherapy

Before and after neoadjuvant chemotherapy (NAC), clinical examination and color Doppler ultrasound were used to judge the change of maximum tumor diameter. The same patients were compared using the same methods before and after chemotherapy, primarily based on clinical examination. Evaluation was carried out once every 3~4 weeks. According to the uniform standards set by WHO, curative effects were divided into: complete remission (CR): complete disappearance of visible lesions, including the axillary lymph nodes; partial remission (PR): tumor shrank by more than 50%; stable (SD): tumor size shrank by less than 50% or increased by less than 25%; Progress (PD): one or more lesions increased by more than 25% or new lesions occurred. The total effective rate was CR + PR (RR).

Immunohistochemistry and FISH detection and standard for molecular typing

All tissues of breast cancer cases were made into paraffin sections and cut into 4um. SP immunohistochemistry method was used to examine the expression of ER, PR, and Her-2/neu in breast cancer tissue.

ER, PR and Her-2/neu monoclonal antibody, anti-mouse SP kit (secondary antibody to it was the rabbit anti-mouse) and DAB kit were purchased from the Maixin biotechnology company in Fijian. SP immunohistochemistry method was used in accordance with product instructions strictly. PBS was the negative control instead of primary antibody, and the breast cancer was the positive control. IHC staining sections were observed with the optical microscope, and were read by professional pathologists. ER and PR were positive cell membrane and scored by semi-quantitative; Her-2/neu was cell nucleus positive, 3+ was positive, 0 was negative, 1-2 + undergo FISH detection.

GLP HER2/CSP17 probe kit was purchased from Beijing Jinpujia Medical Technology Co., Ltd. FISH was performed following the operation instructionl with probe denaturizing, tissue degeneration, hybridization, washed, stained and other steps. Hybridization signals were observed by professional pathologists under the fluorescence microscope. Ratio <1.8 suggested that there is no HER2 gene amplification in the samples. Ratio> 2.2 suggested that HER2 gene amplification occurred in the samples. When Ratio> 20 or many signals clustered, it is considered as gene amplification; When the ratio was between 1.8 and 2.2, number of cells counted could be increased to l00, or this experiment will be repeated to determine the final result (Figure 1).

Breast cancers were divided into four kinds of phenotype according to the criteria of Carey et al. in this study: luminal A (ER+ and/or progesterone receptor positive [PR+], HER2−), luminal B (ER+ and/or PR+, HER2+), HER2+/ER− (ER−, PR−, and HER2+), basal-like (ER−, PR−, and HER2−).

Serum insulin detection

Fasting serum insulin and serum insulin C peptide level were detected by radioimmunoassay method with RIA kit (Tianjin nine tripods medical& bioengineering Co., Ltd). Normal fasting venous serum insulin concentrations are 5-25mIU/mL.

Follow-up

Starting time for follow-up was that when surgery started, and the deadline of follow-up was March 1, 2011. Patients were notified by the physician with telephone and that outpatients were clinically rechecked. 298 patients received follow-up and loss rate of follow-up was 2.3% (7/305). Local or regional recurrence meant clinical or histological recurrence of ipsilateral breast or regional lymph nodes. Distant metastasis refers to lesions that had a relation with tumors in the distance

showed in the clinical and imaging studies. Disease-free survival times were the time from the first day after surgery to the time of first recurrence or metastasis. Total survival times were the time from the first day after surgery to death or the last follow-up.

Statistical analysis

All data were processed using SPSS 13.0 software for windows. Measurement data was showed as mean ± standard deviation ($\chi \pm s$) using t test, and enumeration data were analyzed using $\chi 2$ test. Survival rate in each group were analyzed using Kaplan-Meier curve of each group. Statistical difference of survival between the groups was analyzed using the log-rank test and $P < 0.05$ was considered statistically different.

Results

Clinical characteristic of breast cancer in patients with diabetes mellitus

The ages of 105 cases breast cancer patients in the diabetes mellitus group were from 36 to 79 years old, and the average age was 57.2. 105 cases included 81 invasion ductal carcinoma,five invasive lobular carcinoma, three mixed histological type of carcinoma, four papillary carcinoma, two neuroendocrine carcinoma, two apocrine carcinoma, one medullary carcinoma, one secretory adenocarcinoma, one cribriform carcinoma, two mucinous carcinoma and three ductal carcinoma in situ (DCIS). Of the 105 patients, tumor size of 11 cases was 0-2 cm. Tumor size of 66 cases was 5 cm and tumor size of 28 cases was bigger than 5 cm. According to the standard for clinical breast cancer grading from Union for International Cancer Control, there were 3 cases with stage 0, 7 cases with stage I, 23 cases with stage IIA, 44 cases with stage IIB, 15 cases with stage IIIA, 6 cases with stage IIIB, and 7 cases with stage IIIC. There were 1 case with stage I, 34 cases with stage II and 46 cases with stage III according to the pathology grading. According to the surgical procedures: 17 cases underwent conventional radical mastectomy, 79 cases underwent modified radical mastectomy, four cases underwent breast conservation surgery, three cases underwent total mastectomy, one case underwent segmental mastectomy, one case received non-surgical treatment. No lymph n ode metastasis occurred in 57 cases, 1 ~3 lymph node metastasis occurred in 18 cases, 4 to10 or more lymph node metastasis occurred in 18 cases, more than 10 lymph node metastasis occurred in 11 cases. After surgery, 85 cases received systemic intravenous chemotherapy, including 3 cases for CMF, 53 cases for FEC/CTF and 29 cases for ET. Three cases received oral chemotherapy, and 11 cases did not receive chemotherapy. Fasting serum insulin and 2-h serum insulin in breast cancer patients in the diabetes mellitus group were higher than normal serum insulin concentrations. These clinical data were shown in Table 1.

Molecular phenotype

The immunohistochemistry results of HER-2 in 15 cases in the diabetes group and 25 cases in the control group were 1-2 + with FISH testing. FISH test was positive with 26.7% (4/15) in the diabetic group and 28% (7/25) in the control group. FISH test was negative with 73.3% (11/15) in diabetic group and 72% (18/25) in the control group. There were 48.6% (51/105) with luminal A type, 20.9% (22/105) with luminal B type, 6.7% (7/105) with HER-2 over-expression-type, 23.8% (25/105) with basal-like type in 105 breast cancer patients in the diabetic group. In the control group of 200 patients with breast cancer, there were 45.5% (91/200) with luminal A type, 14.5% (29/200) with luminal B type, 11% (22/200) with HER-2 over-expression-type, 29% (58/200) with basal-like type. There was no significant difference in the molecular phenotype of patients between the diabetes group and control group ($P > 0.05$, Table 1).

Table 1. Analysis of the Clinical Breast Cancer Data in Diabetic and Non-diabetic Patients

	DM group	Control group	P
Age(mean±SD)	57.2±21.8	45.5±15.5	<0.001
Menopausal status			
premenopausal	30	115	<0.001
Postmenopausal	75	85	
Tumor size			
~2cm	11	36	0.1884
2~5cm	66	121	
5~cm	28	43	
Histology			
IDC	81	156	0.8643
other	24	44	
Stage			
early	33	92	0.0140
advanced	72	108	
Pathological Grade*			
I	1	15	0.0069
II	34	75	
III	46	66	
Lymph node metastasis**			
0	35	94	0.0299
0~4	34	51	
4~10	23	37	
10~	11	18	
chemotherapy			
Yes	88	187	0.0069
no	17	13	
Molecular Typing			
Luminal A	51	91	0.2730
Luminal B	22	29	
HER-2	7	22	
Base-like	25	58	
Neo-adjuvant chemotherapy			
CR+PR	27	69	0.0238
SD+PD	13	12	

*Pathological Grade only analyze for IDC; **There are two patients without radical surgery in the DM group and one in the control group.

Table 2. Prognosis Analysis of Breast Cancer Patients in DM Group and Control Group

Outcome	DM group	Control group	Log-rank χ2	P
Breast cancer events				
Local recurrence	8	10		
Distant recurrence	12	17		
Disease free survival	80.2% (81/101)	86.3% (170/197)	6.324	0.012
All-cause mortality				
Breast cancer	8	11		
Heart disease	2	3		
Other	6	1		
Overall survival	84.2% (85/101)	92.4% (182/197)	9.028	0.003
	91.4% (85/93)*	94.3% (182/193)*	2.561	0.110

*Overall survival after removing the other causes of death in breast cancer patients

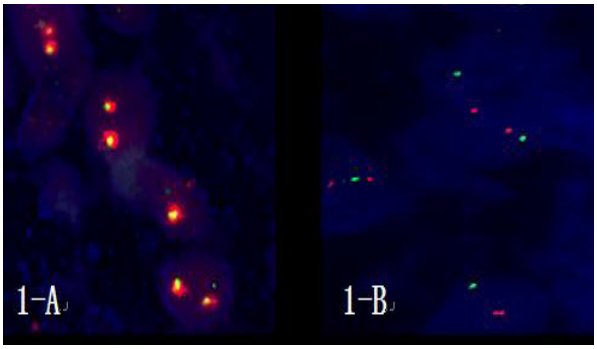

Figure 1 a) HER-2/neu DNA Amplification in Breast Carcinoma by FISH with HER-2/neu Signals/CEP 17 Signal R atios of >2.2; b) Non-amplified HER-2/neu DNA with Ratios <1.8 (1000×)

Curative effects of Neoadjuvant chemotherapy

Forty patients (three cases with CR, 24 cases with PR, 12 cases with SD, one case with PD) underwent preoperative chemotherapy in the diabetes group, and the effective rate of chemotherapy was 62.5% (27/40). 81 patients underwent preoperative chemotherapy (8 cases with CR 61 with cases PR, 11 cases with SD, one case with PD) in the control group, and the effective rate of chemotherapy was 85.1% (69/81). There was a significant difference in the effective rate of chemotherapy between the diabetes group and control group (P <0.05, Table 1).

Prognosis analysis

101 cases of 105 cases had complete follow-up data which follow-up time was 4 to 75 months in the diabetic group, and the median follow-up time was 25 months. Among 101 cases, there were 6 deaths due to complications of diabetes, two sudden deaths due to cardiovascular and cerebrovascular diseases, eight deaths due to breast cancer, five patients with local chest wall recurrence, three cases with contralateral breast recurrence, four patients with bone metastasis, three cases with liver metastasis, one case with lung metastases, four cases with multiple organ distant metastasis. 197 cases of 200 cases had complete follow-up data which follow-up time was 1 to 75 months in the control group, and the median follow-up time was 29 months.

Among 197 cases, there was one death due to car accident, three sudden deaths due to cardiovascular and cerebrovascular diseases, 11 deaths due to breast cancer, seven patients with local chest wall recurrence, three cases with contralateral breast recurrence, seven patients with bone metastasis, three cases with liver metastasis, two cases with lung metastases, five cases with multiple organ distant metastasis.

Disease-free survival (DFS) and overall survival (OS) curve of breast cancer patients between the diabetic group and control group were analyzed using Kaplan-Meier analysis (Figure 2). The results showed that the disease-free survival and overall survival of the diabetic group were worse than the control group, and there was significant difference between the two groups. After excluding patients with other causes of death, overall survival in the diabetic group was worse than that in the control group, but there was no statistically significance (P> 0.05, Table 2).

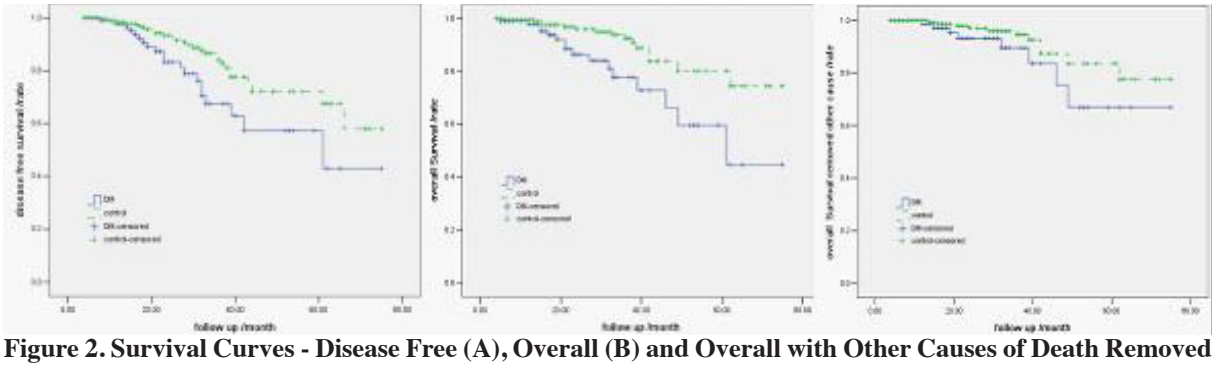

Figure 2. Survival Curves - Disease Free (A), Overall (B) and Overall with Other Causes of Death Removed (C) for Breast Cancer Patients in the DM and Control Groups

Discussion

With the development of human gene expression profiling analysis and molecular biology techniques, people have a better understanding of pathogenesis and treatment strategy of breast cancer, and comprehensive treatment of breast cancer goes into the new era of individualized treatment. The difference of molecular phenotypes and clinical characteristics of breast tumor will lead to the difference of treatment response and prognosis for its heterogeneity in Evidence-Based Medicine (Shipitsin 2007). Both animal experimental and epidemiologic studies have found that type 2 diabetes (T2D) increased breast cancer risk and mortality (Schott et al., 2010; Novosyadlyy et al., 2010). There were special clinical biological characteristic and prognosis in breast cancer in patients with type 2 diabetes.

This study showed that the average age was older (57.2 ± 21.8 years), and proportion of postmenopausal patients were higher (71.4%). Clinical staging were later and the proportion of advanced breast cancer was 68.57%. Lymph node metastasis was more and the proportion of lymph node metastasis was 66.01% in breast cancer patients in the diabetic group. The results were in accordance with results reported by Liao and Erickson (Liao et al., 2010; Erickson et al., 2011). Additionally, this study also showed that majority of histological grade in diabetic patients with breast cancer was II + III-class (98.8%), in accordance with the results of the large sample study from the United States (Nyholm et al., 1989). The effects of diabetes on diagnosis and treatment for breast cancer patients were analyzed by Srokowski et al (Srokowski et al., 2009). It was pointed out that too much attention had been paid to the mellitus diabetes so that the breast cancer screening was neglected, and that diabetic patients had a low level of education (Srokowski et al., 2009). The patients in this study were from China, and early breast cancer screening in China has just begun, so the discovery proportion of breast cancer through screening is still very low. The majority of breast cancer patients with diabetes mellitus saw a doctor because the symptoms were felt by themselves, which were not the reasons of later clinical stage of breast cancer and more lymph node metastasis in the diabetic group with breast cancer. However, in this study, the average age was older in patients with diabetes and the proportion of elderly patients was bigger. The proportion of older persons receiving education in China is generally lower than that in Western countries, and is also lower than the breast cancer patients in general people. Therefore, the age composition in patients in the diabetic group with breast cancer may be one reason of the later clinical stage and more lymph node metastasis.

Prognosis of breast cancer patients with the different molecular phenotype was different, and the prognosis of the triple-negative breast cancer patients is the worst. Prognosis of diabetic patients with breast cancer was poor, and there may be different molecular phenotypes in these patients. However, the present study showed that there was no significantly difference in molecular phenotype between diabetic group and the control group ($P>0.05$). Triple-negative breast cancer rates were 23.8% (25/105) and 29% (58/200) in the diabetic group and the control group, in accordance with the reported results (Peairs et al., 2011).

Erickson et al. reported that poorer prognosis occurred in patients with chronic high blood sugar, and overall survival rates were even lower than that in the control group (Nyholm et ai., 1989). The curative effects of neoadjuvant chemotherapy on breast cancer patients in diabetes and control group were retrospectively analyzed in this study, and it was found that effective rate of chemotherapy for breast cancer patients with diabetes mellitus was 62.5% (27/40). Compared with the control group with 85.1% (69/81), there was significant statistical difference ($P <0.05$). The recently survival analysis found that disease-free survival and overall survival rate in diabetes group were worse than that in the control group, and there were significant differences between the two groups, in accordance with the reported results (Barone et al., 2008; Guastamacchia et al., 2003; Liao et al., 2010; Schrauder et al., 2011;). Pasanisi et al considered that high metabolic syndrome was the risk factor in breast cancer patients with poor prognosis and recurrence (Pasanisi et al., 2006), and the Emerging Risk Factors Collaboration Coordinating Group proposed that diabetes and high blood glucose is an independent risk factor for cancer patients to death (Seshasai et al., 2011). The results in the present study also showed that after excluding patients with other causes of death, overall survival results were worse in the diabetic group, but there was no statistically significance ($P>0.05$). There are possible explanations for these results. One explanation is that there were more complications of diabetic and cardiovascular in diabetic patients in the breast cancer group, causing more accidental death. The results also showed that fewer breast cancer patients received chemotherapy in the diabetes group, leading to poor prognosis of breast cancer. Another explanation is that the smaller sample size, shorter follow-up time, and the adverse effect on the "poor prognosis of breast cancer patients in the diabetic group" caused by lack of anti-tumor treatment or treatment over in this study, which could lead to analysis bias.

The relationships between hyperinsulinemia and breast cancer prognosis were further analyzed. Fasting and 2-hour postprandial serum insulin of 105 cases of breast cancer patients with diabetes mellitus were higher than the normal value, and serum insulin levels in the control group changed in the normal fluctuation range, indicating that hyperinsulinemia might be an important factor for poor prognosis in the diabetic group with breast cancer patients. Some studies reported that

diabetes could promote the occurrence and progression of breast cancer through hyperinsulinemia (Nyholm et al., 1989; Pisani 2008). Insulin specifically binds to the α subunit of insulin receptor (insulin receptor, IR) to activate IR , then activated 3-phosphatidylinositol kinase (PI-3K) pathway and the Ras-MAPK pathway which play a role in mitogenic and antiapoptotic effects, and induced the growth of breast cancer cells to form breast cancer by changing the sex hormone environment (White 2003).

In Goodwin's study, fasting insulin levels in patients with breast cancer were tested, and comparative analysis of clinical and pathological features were carried between breast cancer patients with high insulin levels and normal insulin levels. The pathological features in breast cancer patients with high insulin levels were similar to the results of this study (Goodwin 2002).

In summary, there were more elderly postmenopausal patients, higher percentage of high pathological grade, more lymph node metastasis, and even later clinical stages in the diabetic group with breast cancer than in the control group. However, there was no significant difference in tumor size and molecular phenotype between the diabetic group with breast cancer and the control group. Diabetes is risk factors for poor prognosis of breast cancer patients, and hyperinsulinemia might be an important reason for poor prognosis of breast cancer in the diabetic group.

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