RESEARCH COMMUNICATION

Type 2 Diabetes Mellitus and Characteristics of Breast Cancer in China

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Abstract

Studies have showed an association between type 2 diabetes and breast cancer in Western countries. The association should be confirmed in an Asian population which has a lower incidence of breast cancer. Our study aimed to compare the clinicopathologic characteristics of breast cancers in women with and without type 2 diabetes mellitus in China. Each group included 143 cases, similar in parity, body mass index, family history, mode of diagnosis, menarche age and hormone receptors except for progesterone receptor (PR). The diabetic patients were older, with a mean age of 58.3±10 years and the percentage of postmenopausal patients was 52%, which was higher than non-diabetic patients. Significant differences were found in tumor stage, the amounts of lymph node and with metastasis, these persisting after adjustment for age. Furthermore, a positive association with higher TNM status and PR negative rate was noticed in premenopausal but not postmenopausal diabetic patients. Our results indicate that type 2 diabetes mellitus is a negative prognostic factor for breast cancer, especially in premenopausal women.

Keywords: Breast cancer - diabetes mellitus - characteristics - stage

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Introduction

Breast cancer is the most common cancer among women in recent years.In America,the incidence of breast cancer is just a little lower than non-melanomatous skin cancers,and its mortality rate is second to lung cancer (Carol DeSantis and Melissa M, 2010). Many studies identified that there is an association between diabetes and breast cancer.Up to 18-20% breast cancer patients suffering from diabetes (Khan et al., 2006; Lipscombe et al., 2006; Susanna et al., 2007).

Like breast cancer, Diabetes mellitus also represents common health concern. It affects 9.7% people in the world (CDC, 2005). Type 2 diabetes accounts for 90-95%, its character include insulin resistance, hyperinsulinemia in early phase,and lack of insulin which was caused by beta cell decompensation in terminal phase.

Most studies on the association between diabetes and breast cancer were conducted in the Western world, data from Asian countries are still deficient. Inconsistent results have also been found in Asian populations (Wu et al., 2007). Furthermore,there are few reports in the world which show the relationship between diabetes and the characteristic of breast cancer,especially in Asia. In this study, we have investigated the relationship between type 2 diabetes mellitus and clinicopathologic characteristics of diabetic breast cancer.

Patients and Methods

Study population

The data of our study population include 286 patients aged 29-77 years who were treated in Renmin Hospital, Zhongnan Hospital and Hubei Tumor Hospital,Wuhan, China, between January, 2005 and June, 2009. All patients with breast cancer were diagnosed by pathological examination, and the diagnosis of diabetes mellitus was confirmed,according to the definitions of the WHO, by the presence of fasting glucose levels of above 7.1mmol/L in routine laboratory evaluation (WHO, 1999). Each diabetic patient was matched to one non-diabetic female breast cancer patients who were diagnosed at the closest date. Eliminate the patients who was accompanied with other malignant tumor. Finally, all patients included in our study had complete data and systemic treatment.

Data collection

A complete clinical and pathological data were reviewed. The clinical data were reviewed for age,body mass index,menopausal status, menarche age, breast cancer family history and pregnancy history. And the patients record also include the mode of breast cancer diagnosis, type of surgery, chemotherapy, hormonotherapy, diabetes diagnosis, the corresponding age of onset and the use of hypoglycemic agents. The pathological data

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include tumour histology, size, lymph node condition, oestrogen receptor (ER), progesterone receptor (PR) and Her-2 status.

Statistical analysis

Using SPSS11.5 software for statistical analysis, and calculated the mean and SD for every parameter. Univariate conditional logistic regression was used to examine the difference in the distribution of patients'characteristics as well as clinical and tumour characteristics, where the stratum variable was the unique number identifying each matched set. A value of $p<0.05$ (two sided) was chosen as the limit of significance.

Results

Patients' general conditions

All breast cancer patients had surgical treatment, chemotherapy, endocrine therapy,and most diabetic patients were treated by oral hypoglycemic agents or insulin.

Patients' general conditions were present in Table 1. The mean age of diabetic patients was 58.3±10.0 years old,and there were 52% postmenopausal patients in this group which was significantly higher than non-diabetic breast cancer patients'group ($p<0.001$). Both groups were well balanced on body mass index, parity, age of menarhe and family history of breast cancer among first-degree relatives. Nearly 50% of patients in both groups went to hospital because of symptoms,and about one-quarter patients were diagnosed breast cancer by mammography. There is no difference in both group.

Table 1. Patients' General Conditions

	Diabetic N=143	Non-diabetic N=143	Overall P
Age(mean±SD)	58.3 ±10.0	49.1±11.7	<0.001
Menarche	14.0±1.6	14.0±1.7	0.723
BMI	27.1±3.8	26.9±4.0	0.765
Parity (N%)			0.325
0	5 (3)	2 (2)	
1	50 (35)	65 (45)	
2	60 (42)	52 (36)	
3+	28 (20)	24 (17)	
Family history			
Positive	7 (5)	1 (1)	
Negative	136 (95)	142 (99)	
Menopausal status			<0.001
premenopausal	69 (48)	115 (80)	
Postmenopausal	74 (52)	28 (20)	
Diagnosis			0.3580
Symptoms	70 (49)	66 (46)	
Screening	36 (25)	41 (29)	
Unknown	37 (26)	36 (25)	

Table 2. Pathological Characteristic of Breast Cancers in Diabetic and Non-diabetic Patients

	Diabetic N=143	Non-diabetic N=143	Overall P
Stage			<0.001
1	25 (17%)	32 (23%)	
2	60 (42%)	83 (58%)	
3	45 (32%)	3 (2%)	
4	13 (9%)	3 (2%)	
T			0.057
1	37 (26%)	49 (34%)	
2	80 (56%)	72 (50%)	
3	18 (13%)	21 (15%)	
4	8 (5%)	1 (1%)	
N			<0.001
0	62 (43%)	81 (57%)	
1	31 (22%)	49 (34%)	
2	41 (29%)	3 (2%)	
3	9 (6%)	10 (7%)	
M			0.010
0	130 (91%)	140 (3%)	
1	13 (9%)	3 (2%)	
Stage			<0.001
Early	79 (55%	117 (82%)	
Advanced	64 (45%)	26 (18%)	

Pathological characteristic of breast cancer

There is a significant difference in the distribution of tumor stage (Table 2). While 41% of the diabetic patients were diagnosed with stage III/IV disease, only 19% of the non-diabetic patients were diagnosed at those stages ($p<0.001$). Diabetic patients have a higher rate of lymph node metastasis(Diabetic group N2/N3 versus non-diabetic group N2/ N3,35% vs 9%, $p<0.001$), and diabetic breast cancer patients are more prone to metastasis. If analyze the stage by early (T1/2, N0/1 and M0)versus advanced disease (T3/4, N2/3 or M1) we could found that there are significantly more diabetic patients diagnosed with advanced disease compared to the non-diabetic patients (45% vs. 18%, $P<0.001$)

The biological characteristics of breast cancer was showed in Table 3.Significant differences in the distribution of progesterone receptor were noticed.If we didn't consider the part of unknown,the rate of PR-positive in diabetic group are higher than non-diabetic group ($p=0.004$).

Stratification by menstruation status

As menopausal status may affect the pathological features of breast cancer, we conducted an analysis according to menstruation status(Table4, Table5) and found that premenopausal diabetic patients not only have a higher T stage (T3+4 versus T1+2 between diabetic and non-diabetic group, RR=1.53,95%CI 0.72-

Table 3. Histology and Hormone Receptors of Breast Cancer in Diabetic and Non-diabetic Patients

	Diabetic N=143	Non-diabetic N=143	Overall P
ER status			0.700
Positive	75 (53%)	86 (60%)	
Negative	62 (43%)	46 (32%)	
Unknown	6 (4%)	11 (8%)	
PR status			<0.001
Positive	81 (56%)	106 (74%)	
Negative	56 (39%)	35 (24%)	
Unknown	6 (5%)	2 (2%)	
HER-2 status			
Positive	62 (43%)	72 (50%)	
Negative	64 (45%)	71 (50%)	
Unknown	17 (12%)	0 (0%)	
Histology			0.774
IDC	113 (79%)	111 (78%)	
Other	30 (21%)	32 (22%)	

Table 4. Clinicopathological Characteristics and Hormone Receptors of Breast Cancer in Diabetic and Non-diabetic Postmenopausal Patients

		Diabetic N=143	Non-diabetic N=143	Overall P	RR	95% CI
T	1	27 (36)	15 (54)	0.161	1.3[0b]	0.33-5.13[b]
	2	37 (50)	10 (36)			
	3	8 (11)	3 (10)			
	4	2 (3)	0 (0)			
N	0	42 (56)	16 (56)	0.298	3.59[c]	0.77-16.8[c]
	1	16 (22)	10 (36)			
	2	8 (11)	1 (4)			
	3	8 (11)	1 (4)			
M	0	67 (91)	27 (96)	0.324	2.82	0.33-23.8
	1	7 (9)	1 (4)			
ER status				0.360[a]	0.66	0.27-1.62
Positive		38 (51)	11 (39)			
Negative		34 (46)	15 (54)			
Unknown		2 (3)	2 (7)			
PR status				0.464[a]	0.71	0.29-1.77
Positive		35 (47)	11 (39)			
Negative		34 (46)	15 (54)			
Unknown		5 (7)	2 (7)			
HER-2 status				0.637[a]	1.24	0.50-3.09
Positive		30 (40)	16 (57)			
Negative		28 (38)	12 (43)			
Unknown		16 (22)	0 (0)			

[a]Calculated without unknowns; [b]T3+4 vs T1+2; [c]N2+3 vs N0+1

Table 5. Clincopathological Characteristics and Hormone Receptors in Breast Cancer in Diabetic and Non-diabetic Premenopausal Patients

		Diabetic N=143	Non-diabetic N=143	Overall P	RR	95% CI
T	1	10 (14.5)	34 (30)	0.008	1.55[b]	0.72-3.21[b]
	2	43 (62)	52 (54)			
	3	10 (14.5)	18 (15)			
	4	6 (9)	1 (1)			
N	0	20 (29)	65 (56)	<0.001	9.18[c]	0.77-16.75[c]
	1	15 (21)	39 (34)			
	2	33 (49)	2 (2)			
	3	1 (1)	9 (8)			
M	0	63 (91)	113(98)	0.025	5.38	0.33-23.8
	1	6 (9)	2 (2)			
ER status				0.065[a]	1.83	0.27-1.62
Positive		37 (54)	75 (65)			
Negative		28 (40)	31 (27)			
Unknown		4 (6)	9 (8)			
PR status				0.014a	2.27	1.13-4.58
Positive		46 (67)	95 (83)			
Negative		22 (32)	20 (17)			
Unknown		1 (1)	0 (0)			
HER-2 status				0.830a	1.07	0.50-3.09
Positive		32 (46.5)	56 (49)			
Negative		36 (52.5)	59 (51)			
Unknown		1 (1)	0 (0)			

[a]Calculated without unknowns; [b]T3+4 vs T1+2; [c]N2+3 vs N0+1; RR, relative risk; CI, confidence interval

Table 6. Clinicopathological Characteristic and Hormone Receptors of of Breast Cancer, Adjusted for Age

		Diabetic N=143	Non-diabetic N=143	Overall P	RR	95% CI
T	1	20 (21)	33 (34)	0.023	1.42[b]	0.67-2.98[b]
	2	57 (59)	49 (51)			
	3	13 (13)	14 (14)			
	4	7 (7)	1 (1)			
N	0	32 (33)	57 (59)	<0.001	16.32[c]	5.54-48.0[c]
	1	25 (26)	36 (37)			
	2	35 (36)	1 (1)			
	3	5 (5)	3 (3)			
M	0	89 (91)	96 (99)			1.06-70.4
	1	8 (9)	1			
ER status				0.266[a]	1.40	0.77-2.53
Positive		52 (54)	60 (62)			
Negative		40 (41)	33 (34)			
Unknown		5 (5)	4 (4)			
PR status				0.023[a]	2.10	1.13-3.89
Positive		55 (57)	71 (73)			
Negative		39 (40)	24 (25)			
Unknown		3 (3)	2 (2)			
HER-2 status				0.056[a]	1.76	0.98-3.14
Positive		38 (39)	55 (57)			
Negative		51 (53)	42 (43)			
Unknown		8 (8)	0 (0)			

[a]Calculated without unknowns; [b]T3+4 vs T1+2; [c]N2+3 vsN0+1; RR, relative risk; CI, confidence interval

3.21), but also have more lymph node metastasis (N2+3 versus N0+1 between diabetic and non-diabetic group, RR=9.18, 95% CI 4.21-20.04, P<0.001) and distant metastasis (M1 versus M0 between diabetic and non-diabetic group, RR=5.38, 95% CI 1.06-27.71, P=0.025). What's more, premenopausal diabetic patients with breast cancer are often ER, PR, HER2 negative compared with control group, but only PR have significant difference (RR=2.27,95%CI 1.13-4.58,P=0.014). Both groups among postmenopausal patients were balanced not only on T N M status but also on ER, PR, HER2 status.

3.4 Adjustment of diabetes mellitus effects for age

As age is another major confounding factor between diabetes and breast cancer, we conduct another analysis after we adjusted and balanced the age in both group. The results were presented in Table 6. We can see that diabetic group has a higher TNM status compared with non-diabetic group, and the difference has statistical significance (p=0.023, <0.001, and 0.017 for T, N, M status, respectively). After adjusting for age, breast cancer patients with diabetes were still more often PR negative (RR=2.10, 95% CI 1.13-3.89, P=0.018).

Discussion

We study the characteristics of breast cancer in patients with and without diabetes, The result provide evidence that type 2 diabetes mellitus may adversely alter the presentation of breast cancer.Our study data suggest that more patients in diabetic group were

postmenopausal,and this group presented with more advanced stage and higher rate of lymph node metastasis. Furthermore, breast cancer in diabetic group was more PR negative. And the significant difference still exist even after adjusting for age. We analyzed the impact of different menstrual status on clinicopathological characters, and found that premenopausal diabetic patients have higher TNM status and more negative PR status than non-diabetic premenopausal patients. But we didn't found significant difference among the postmenopausal patients.

Before discussing the significance of these findings, several study limitations should be mentioned.First, the sample size of study population was a small group of 286 patients. This may cause some errors. Several study whose total sample size of study population is larger than our study suggest diabetic patients were always ER negative (Papa et al., 1990; Wolf et al., 2006). Another limitation is that the information on diabetes was based on fasting blood-glucose and self-report of conditions that were diagnosed by a physician. And some patients may be misclassified, which will only decrease the differences between the two groups. Even if our study have some limitations,it still prove diabetes is a negative prognostic factors for breast cancer in Chinese population.

In our study, we found that breast cancer with diabetes were more likely to occur in old and postmenopausal women, which is similar to Yanclk's (Yancik R et al.,2001) conclusion. It is necessary for old diabetic patients to do mammography every year. It is also very important for premenopausal diabetic patients to do a breast examination each year. As our study showed that premenopausal diabetic patients with breast cancer had a poorer prognosis compared with non-diabetic premenopausal patients. Our study also show that there are significant difference in tumor stage and rate of lymph node metastasis. It is the same as Wolf (Wolf I et al., 2006) and Guastamacchia (Guastamacchia E et al,2003). The present researches are controversial on the expression of the hormone receptors. The study of Wolf (Wolf I et al., 2006) and Papa V (Papa et al., 1990) showed that breast cancer among most diabetic patients were more often ER,PR negative, while other study didn't find out significant difference (Guastamacchia et al., 2003; Rollison et al., 2008).

Diabetes can change breast cancer's characteristics and outcome through biological mechanisms directly or indirectly. Several hypothetic mechanisms may explain the potential role of diabetes plays in changing the clinicopathological characters of breast cancer. The potential biochemical mechanisms include activation of the insulin pathway, activation of the insulin-like-growth-factor pathway, regulation of endogenous sex hormones and so on.

Insulin have a similar structure with insulin-like growth factor 1 (IGF-1), and both of them were powerful mitogenic agents, which presented in both normal and tumor breast tissue and promote mitosis in both of them (Cust et al 2009; Call et al., 2010; Novosyadlyy et al 2010). Meanwhile, Insulin can also increase the biologic activity of IGF-1 and decrease the production of IGF-binding proteins (Goodwin et al., 2002; Garmendia et al., 2007). Furthermore,Insulin can also activate phosphatydylinositol 3-kinase, which in turn activates the AKT pathway, and the AKT pathways have important roles in tumorigenesis (Cseh et al, 2009). Some study showed that Hyperinsulemia is associated with high concentration of estrogen and low levels of sex hormone binding globulin (SHBG), which leads to an increase in the bioavailability of estradiol. (Stoll, 2002; Williams, 2010). Insulin, IGF-1 and estrogen have an synergistic effect on the growth and proliferation of tumor cell, and young women (most are premenopausal women) are more likely to have high levels of estrogens,which could explain why premenopausal diabetic patients have a higher stage in TNM status than non-diabetic patients compared with postmenopausal patients in our study. As we know,hyperglycemia which was caused by diabetes also promote tumor cell's growth and proliferation (Krone and Ely, 2005; Dankner et al., 2007). Finally,Leptin and adiponectin may be another potential pathway. Recent studies show that increased leptin and decreased adiponectin levels have been observed in type 2 diabetic patients, which will help the development of breast cancer (Barb et al., 2007; Karaduman et al., 2007; Bartella et al., 2008; Kaklamani et al., 2008).

Our research shows that even in Asia where the incidence of breast cancer is the lowest, diabetes is associated with negative prognostic factors. The biological mechanism is still unclear. Present studies still have a lot of limitations, there's a lot of rigorous work to do find out the exact relationship between diabetes and breast cancer,especially for its biological mechanisms.

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