Relationship between Diabetes Mellitus and Clinicopathological Stages of Breast Cancer at Diagnosis

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Abstract:

Diabetes is a risk factor for development of specific neoplasms, including breast cancer. Women with type-2 diabetes mellitus (T2DM) are at increased risk for developing breast cancer. Breast cancer subtypes have been extensively studied, but few studies have examined whether diabetic women present with more advanced breast cancer stages. **Aim of study**: evaluate whether T2DM has effect on clinicopathological stages of breast cancer at diagnosis. **Subjects and methods**: 102 breast cancer women were studied, 51 had T2DM and 51 were non-diabetic. Clinical assessment, BMI, FBS, 2-hPPBS, HbA1c level, total cholesterol, triglyceride, C-peptide, breast mammography, and body imaging and scanning were performed. Biopsy samples from breast tissues were reviewed; histologic morphology and grades were determined. Hormone receptor status (ER, PR, HER2) was determined. Clinical stages of breast cancer were determined based on TNM staging system. **Results**: BMI was significantly higher in type-2 diabetic breast cancer women compared to non-diabetic. Type-2 diabetic breast cancer women had more invasive pathologic subtypes and advanced stages of breast cancer compared to those who were non-diabetic. Breast cancer women with invasive duct carcinoma had significantly higher BMI (32.0±6.1kg/m^2), FBS (130.3±30.4mg/dL), 2-hPPBS (221.6±72.5mg/dL), HbA1c (7.8±2.2%), cholesterol (202.2±39.9mg/dL), and triglyceride (154.9±16.1mg/dL) compared to those with ductal carcinoma in situ. **Conclusion and recommendation**: breast cancer in type-2 diabetic women is often diagnosed at advanced stages and being of more aggressive pathologic subtype. Whether proper control of diabetic status has effect on progression of breast cancer needs further studies.

Key words: breast cancer, clinicopathological stages, diabetes mellitus.

Introduction:

Diabetes is emerging as one of the most prevalent human aliments next to cardiovascular diseases and is the sixth leading cause of death worldwide [1]. A number of studies have related diabetes to cancer risk; furthermore, growing evidences suggested an abnormal glucose homeostasis as an independent risk factor for the development of specific neoplasms [2].

Diabetes mellitus and breast cancer are chronic diseases with increasing incidence in many countries [3]. Women with type-2 diabetes mellitus (T2DM) are at increased risk of developing breast cancer, which is the most common malignant tumor in females [4]. Women with diabetes have a 15-20% increased risk of breast cancer compared to women without diabetes, and breast cancer in women with diabetes is often diagnosed at an advanced stage compared to women without diabetes [5].

Several mechanisms have been suggested for the increased risk of breast cancer among women with T2DM, such as the common risk factors (like obesity), the specific metabolic derangements of diabetes itself (i.e., hyperglycemia, hyperinsulinemia, and insulin resistance) and the sue of insulin and specifically insulin analogs [6].

Hyperinsulinemia in itself, especially present in people with impaired glucose tolerance, may promote tumor cell growth directly via insulin receptors or indirectly via insulin-like growth factor-1 (IGF-1) receptors [7]. IGF-1, and subsequently the IGF-1 receptor, could act as a growth stimulus for tumor cells and increase tumor growth, invasion, and metastases [8].

Women with diabetes have a 40% higher risk of death after breast cancer compared to women without diabetes; the comorbidity and diabetes-related complications may contribute to high all-cause mortality. However, diabetes also increases the risk of breast-cancer-specific deaths [9]. Another reason for the worse breast cancer survival may be that women with diabetes develop a more aggressive or less treatment-responsive tumor subtype. It has been shown that hormone-related breast cancer and diabetes risk factors, such as obesity, are associated with development of estrogen receptor (ER)-negative breast cancer subtypes [3]. Insulin interacts with estrogens; there is experimental support that insulin may enhance estrogen production, stimulating the development of ER-positive breast cancer [10].

Breast cancer subtypes have been extensively studied in the general population [3]. Yet, few studies have examined whether women with diabetes present with more advanced breast cancer stage [9].

Aim of study

The aim of this study is to evaluate whether type-2 diabetes mellitus has an effect on the clinicopathological stage of breast cancer at diagnosis.

Subjects and methods

This study was conducted at Hematology-Oncology Unit, Internal Medicine Department, Benha University Hospital, Egypt, during the period from January 2019 to February 2020 and included 102 patients diagnosed with breast cancer. This study was approved by ethics committee of Benha University Hospital.

Patients were informed about the nature of study and written consents were obtained from them. Adult women, aged 30 years or older, with histopathologic-confirmed unilateral breast cancer, having type-2 diabetic or non-diabetics, and having different body weights were included in present study. Exclusion criteria include younger patients, women with type-1 diabetes mellitus, women with bilateral breast cancers, women with other malignancy, and male patients with breast cancer. The diagnosis of breast cancer and its pathologic subtypes were determined based on the results of breast tissue biopsy samples [11], and the diagnosis of T2DM was made according to American Diabetic Association (ADA), 2014 (based on the patient's age, body weight overweight/obesity, fasting blood sugar "FBS" of 126mg/dL or more, 2-hour post-prandial blood sugar "2-hPPBS" of 200mg/dL or more, random blood sugar "RBS" of 200mg/dL or more, glycosylated hemoglobin "HbA1c" of 6.5% or more, normal or elevated serum insulin and C-peptide levels, and absence of specific antibodies against islet β-cells) [12]. Patients were categorized into two groups: group-A (51 women with T2DM and breast cancer) and group-B (51 non-diabetic women with breast cancer) which was used as a comparison group. All included patients were subjected to full history taking and thorough physical examination. Patients' height, body weight, and body mass index (BMI) were determined. From each patient, venous blood sample (5mL) was obtained from antecubital vein under aseptic technique, centrifuged, and stored for later

determination of various serum parameters, which included FBS level, 2-hPPBS level, RBS level, HbA1c level, serum lipids profile (total cholesterol, low-density lipoprotein "LDL" cholesterol, high-density lipoprotein "HDL" cholesterol, and triglyceride levels), C-peptide, and anti-islets antibodies. Breast mammography was done to confirm the presence of breast mass and to exclude presence of contralateral breast mass. Body imaging and scanning were performed to determine lymph node affects and distant metastases. The breast's biopsy samples were reviewed by expert pathologist to confirm the diagnosis of breast cancer, determine morphology (ductal, lobular, mixed), histologic grades (grade-I "well-differentiated", grade-II "moderately-differentiated, and grade-III "poorly-differentiated"); in addition, hormone receptor status, including estrogen receptor (ER), progesterone receptor (PR), and hormone epidermal growth factor receptor "herpceptin-2" (HER2) was determined [11]. The clinical stages of breast cancer, determined according to the American Joint Committee of Cancer (AJCC) 2017 and based on TNM staging system (T is tumor size; N is lymph nodes status; M is distant metastasis), were categorized into stage-0, stage-I (Ia, Ib), stage-II (IIa, IIb), stage-III (IIIa, IIIb, IIIc), and stage-IV [13].

Statistical methods

Statistical analyses were done using SPSS (Statistical Package of Social Science), version 20 (SPSS Statistics for Windows, version 20; Armonk, New York: IBM Corp., Released 2011). Kolmogorov Smirnov test was done to test the normality of data distribution. Numerical data were expressed as number, mean, and standard deviation (SD). Non-numerical data were expressed as frequency and percentage. Student t-test was used to assess the statistical significance of the difference between means of study groups. Chi-Square test was used to examine the relationship between two qualitative data. Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. All reported p values were two-tailed, and p value less than 0.05 ($P < 0.05$) was considered to be significant [14].

Results

This study was conducted during the period from January 2019 to February 2020 and included 102 breast cancer women, 51 women (50%) had breast cancer and type-2 diabetes and 51 women (50%) had breast cancer but were non-diabetic. The mean age ± SD of type-2 diabetic breast cancer

patients was 47.2±9.2 years and that of non-diabetic breast cancer patients was 45.5±11.1 years with non-significant difference regarding age between type-2 diabetic and non-diabetic breast cancer patients (p value = 0.39) (table 1). Also, table 1 showed that type-2 diabetic breast cancer women, their mean BMI was 34.7±4.5 kg/m^2, cholesterol was 214.2±39.8mg/dL, triglyceride was 159.5±15.8mg/dL, FBS was 145.4±18.1mg/dL, 2-hPPBS was 254.5±54.1mg/dL, and of HbA1c was 9.1±1.4%, which were significantly higher compared to their levels in non-diabetic breast cancer women, with P values of 0.01, 0.001, 0.01, 0.001, 0.001, and 0.001, respectively.

Table 2 showed that HER2 receptor was positive in 11.8% of patients with type-2 diabetic breast cancer and in 9.8% of non-diabetic breast cancer patients, with no significant difference between the two groups (P value = 0.974). The ER receptor was positive in 84.3% of type-2 diabetic breast cancer patients and in 51% of non-diabetic breast cancer patients; the prevalence of ER-positivity was significantly higher in breast cancer patients with type-2 diabetes compared to non-diabetic breast cancer patients (P value = 0.001). The PR receptor was positive in 64.7% of type-2 diabetic breast cancer patients and in 56.9% of non-diabetic breast cancer patients, with no significant difference among the two groups regarding PR-positivity (p value = 0.417). In non-diabetic breast cancer women, ductal carcinoma in situ was found in 64.7% of cases and invasive ductal carcinoma was found in 35.3% of women. On the other hand, 3.9% of women with type-2 diabetes and breast cancer had ductal carcinoma in situ and 96.1% had invasive ductal carcinoma. Significant differences regarding prevalence of pathologic types of breast cancer were reported between type-2 diabetic breast cancer women and non-diabetic breast cancer women (p value = 0.001). Regarding clinical staging of breast cancer, 58.8% of non-diabetic breast cancer women had stage-I disease, 31.4% had stage-II disease, and 9.8% had stage-III disease; on the other hand, 41.2% of type-2 diabetic breast cancer women had stage-II disease, 58.8% had stage-III disease, but none had stage-I disease. Significant differences regarding clinical stages were observed between type-2 diabetic breast cancer women compared to non-diabetic breast cancer women (p value = 0.001) (table 2).

As shown in table 3, breast cancer women with stage-I disease had BMI of 22.8±1.4 kg/m^2, FBS level of 84.8±7.4mg/dL, 2-hPPBS level of 128.3±5.7mg/dL, HbA1c level of 4.8±0.5%, cholesterol level of 165.9±5.4mg/dL, and triglyceride level of 140.0±6.2mg/dL. Breast cancer women with stage-II disease had BMI of 28.2±4.3 kg/m^2, FBS level of 123.1±35.0mg/dL, 2-hPPBS level of 202.7±68.6mg/dL, HbA1c level of 6.9±2.2%, cholesterol level of 194.2±40.2mg/dL, and triglyceride level of 152.5±15.6mg/dL. Breast cancer women with stage-III disease had BMI of 35.3±5.6 kg/m^2, FBS level of 134.2±25.3mg/dL, 2-hPPBS level of 234.0±64.3mg/dL, HbA1c level of 8.5±2.1%, cholesterol level of 207.3±38.8mg/dL, and triglyceride level of 155.4±17.1mg/dL. There were significant differences among breast cancer women with stage-I disease, stage-II disease, and stage-III disease regarding BMI, FBS, 2-hPPBS, HbA1c, cholesterol, and triglyceride levels, with p values of 0.001, 0.001, 0.001, 0.001, 0.001, and 0.01, respectively (table 3).

Table 4 revealed that breast cancer women with ductal carcinoma in situ had BMI of 22.9±1.4 kg/m^2, FBS level of 85.2±7.9mg/dL, 2-hPPBS level of 128.7±5.7mg/dL, HbA1c level of 4.8±0.5%, cholesterol level of 165.7±5.4mg/dL, and triglyceride level of 139.3±5.9mg/dL. Breast cancer women with invasive duct carcinoma had BMI of 32.0±6.1 kg/m^2, FBS level of 130.3±30.4mg/dL, 2-hPPBS level of 221.6±72.5mg/dL, HbA1c level of 7.8±2.2%, cholesterol level of 202.2±39.9mg/dL, and triglyceride level of 154.9±16.1mg/dL. Significant differences were observed between breast cancer women with ductal carcinoma in situ and breast cancer women with invasive duct carcinoma regarding BMI, FBS, 2-hPPBS, HbA1c, cholesterol, and triglyceride levels, with p values of 0.001, 0.001, 0.001, 0.001, 0.001, and 0.01, respectively. Furthermore, significant positive correlations were observed between clinical stages of breast cancer and serum levels of FBS (figure 1), 2-hPPBS (figure 2), and HbA1c (figure 3).

Table 1: various parameters according to diabetic status of breast cancer women

Total number = 102 women

Parameter	Non-diabetic breast cancer women n = 51 (mean±SD)	Type-2 diabetic breast cancer women n = 51 (mean±SD)	P value
Age (in years) (mean ±SD)	45.5±11.1	47.2±9.2	0.39
BMI (kg/m^2) (mean ±SD)	23.4±1.5	34.7±4.5	0.01
Cholesterol (mg/dL) (mean ±SD)	166.6±5.5	214.2±39.8	0.001
Triglyceride (mg/dL) (mean ±SD)	140.1±6.1	159.5±15.8	0.01
FBS mg/dL (mean ±SD)	85.9±8.4	145.4±18.1	0.001
2-hPPBS mg/dL (mean ±SD)	128.6±5.8	254.5±54.1	0.001
HbA1c (%) (mean ±SD)	4.7±0.5	9.1±1.4	0.001

Table 2: frequency and percentage of women according to some parameters

Total number = 102 women

Parameter		Non-diabetic breast cancer n = 51	Type-2 diabetic breast cancer n = 51	P value
HER2 receptor	**Negative (n; %)**	46 (90.2%)	45 (88.2%)	0.974
	Positive (n; %)	5 (9.8%)	6 (11.8%)	
ER receptor	**Negative (n; %)**	25 (49%)	8 (15.7%)	0.001
	Positive (n; %)	26 (51%)	43 (84.3%)	
PR receptor	**Negative (n; %)**	22 (43.1%)	18 (35.3%)	0.417
	Positive (n; %)	29 (56.9%)	33 (64.7%)	
Pathologic subtypes	**Ductal carcinoma in situ (n;%)**	33 (64.7%)	2 (3.9%)	0.001
	Invasive ductal carcinoma (n;%)	18 (35.3%)	49 (96.1%)	
Stages	**Stage-I (n; %)**	30 (58.8%)	0 (0.0%)	0.001
	Stage-II (n; %)	16 (31.4%)	21 (41.2%)	
	Stage-III (n; %)	5 (9.8%)	30 (58.8%)	

Table 3: various parameters according to breast cancer stages

Number = 102 women

Parameter	Stage-I n = 30 (mean±SD)	Stage-II n = 37 (mean±SD)	Stage-III n = 35 (mean±SD)	P value
BMI (kg/m^2)	22.8±1.4	28.2±4.3	35.3±5.6	0.001
FBS (mg/dL)	84.8±7.4	123.1±35.0	134.2±25.3	0.001
2-hPPBS (mg/dL)	128.3±5.7	202.7±68.6	234.0±64.3	0.001
HbA1c %	4.8±0.5%	6.9±2.2%	8.5±2.1%	0.001
Cholesterol (mg/dL)	165.9±5.4	194.2±40.2	207.3±38.8	0.001
Triglyceride (mg/dL)	140.0±6.2	152.5±15.6	155.4±17.1	0.01

Table 4: various parameters according to pathologic subtypes of breast cancer

Number = 102 women

Parameter	Ductal carcinoma in situ n = 33 (mean±SD)	Invasive duct carcinoma n = 69 (mean±SD)	P value
BMI (kg/m^2)	22.9±1.4	32.0±6.1	0.001
FBS (mg/dL)	85.2±7.9	130.3±30.4	0.001
2-hPPBS (mg/dL)	128.7±5.7	221.6±72.5	0.001
HbA1c %	4.8±0.5%	7.8±2.2%	0.001
Cholesterol (mg/dL)	165.7±5.4	202.2±39.9	0.001
Triglyceride (mg/dL)	139.3±5.9	154.9±16.1	0.01

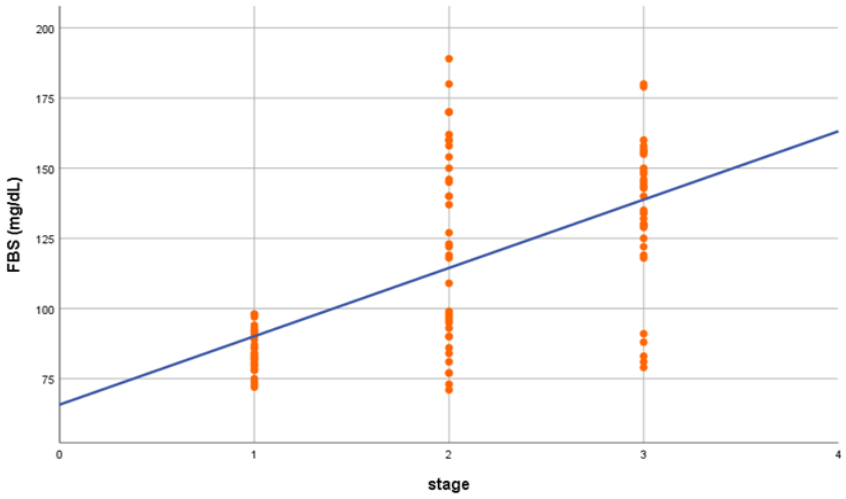

Figure 1: correlation between FBS and breast cancer stages

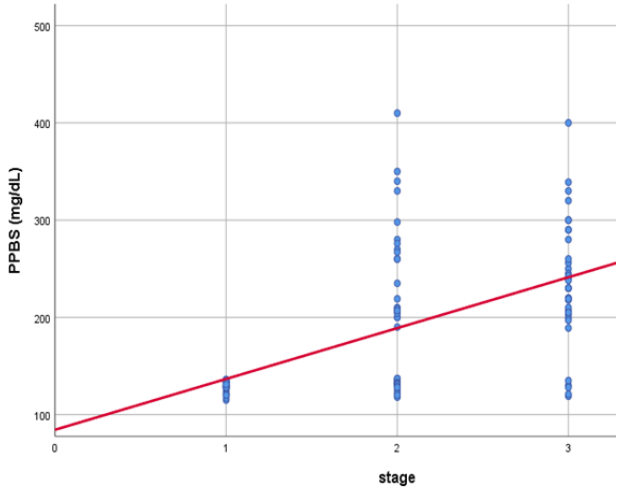

Figure 2: correlation between 2-hPPBS and breast cancer stages

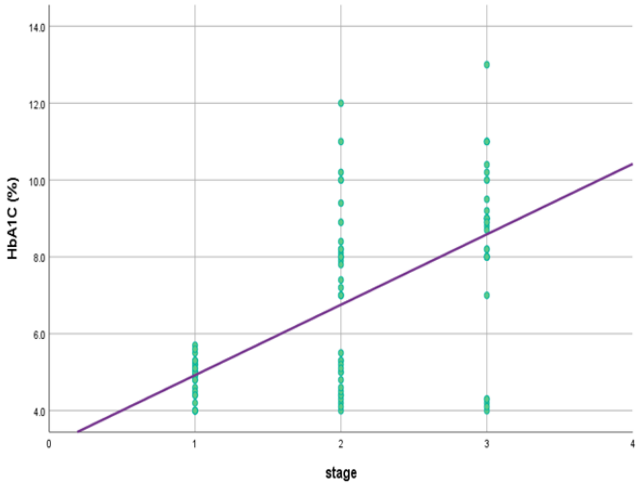

Figure 3: correlation between HbA1c and breast cancer stages

Discussion

Evidence regarding the association between diabetes and breast cancer stages has been mixed; some studies have shown more advanced breast cancer stage among diabetes patients [15], but other failed to find an association [16]. In the present study, type-2 diabetic women with breast cancer had significantly higher BMI, cholesterol, and triglyceride levels compared to non-diabetic breast cancer women. Similarly, a positive association between diabetes and risk of breast cancer has been reported in females [17].

Obesity and diabetes are considered some of the risk factors for the onset of breast cancer; obesity is considered as one of the predisposing factors for cancer even in non-diabetic individuals with impaired fasting glucose levels [1]. Obesity, insulin resistance and chronic inflammation are the characteristic features in metabolic syndrome [18]. Insulin resistance could lead to compensatory hyperinsulinemia, which enhanced the cross-binding of insulin to insulin-like growth factor-1 (IGF-1) receptors expressed on breast epithelial cells; the activated IGF-1 pathway may stimulate the carcinogenesis and progression of cancer [19].

A possible suggested pathway for the association between type-2 DM and breast cancer characteristics is hyperinsulinemia

that might stimulate tumor growth [6]. In the current study, on comparing type-2 diabetic to non-diabetic breast cancer women, there were non-significant differences regarding percentage of HER2 receptor positivity (11.8% vs. 9.8%) as well as percentage of PR-positivity (64.7% vs. 56.9%), but the percentage of ER-positivity was significantly higher in type-2 diabetic breast cancer women compared to non-diabetic breast cancer women (84.3% vs. 51%).

Consistently, differences between cancer subtypes, e.g., 80% versus 60% ER-positive tumors, were reported in women with and without diabetes [3]. Moreover, some studies determined the association between diabetes and hormone receptor status (HER2, ER, and PR) [6].

One study reported a significant association between diabetes and ER receptor [20]. Three studies [5], [15], [20] found that breast cancer among women with diabetes was more often PR-negative; none of these studies reported a significant association between diabetes and HER2 receptor.

The present study showed significant differences regarding pathologic subtypes of breast cancer between type-2 diabetic and non-diabetic breast cancer women, where invasive ductal carcinoma was significantly higher in type-2 diabetic compared to non-diabetic breast cancer women. Concurrently, indolent tumors may progress more rapidly in patients with diabetes, or diabetes may lead to higher metastatic potential [21]. This association in women with longer-duration diabetes further supports a mitogenic effect of diabetes on breast tumors, which would be the most salient in women who were exposed to diabetes for a longer latency period prior to breast cancer diagnosis [22]. In addition, women with type-2 diabetes mellitus were at risk of being diagnosed with a larger tumor, a more advanced lymph nodes status, a more advanced tumor stage, and a higher grade tumor than women without diabetes [6].

In the current study, majority of the type-2 diabetic breast cancer women presented with stage-III disease and none presented with stage-I disease, whereas, the majority of non-diabetic breast cancer women presented with stage-I disease and minority presented with stage-III disease. Consistently, women with diabetes are significantly more likely to present with advanced-stage breast cancer compared to those without diabetes [9]. Other studies demonstrated more advanced stage of breast cancer among women with

diabetes [15], [23]. In addition, women with T2DM are at increased risk to be diagnosed with a more aggressive type of breast cancer than women without [6].

The risk of advanced-stage breast cancer was greatest in younger women and those with longer-standing diabetes; these findings suggest that diabetes may predispose women to more rapidly progressive breast cancer, leading to more advanced-stage disease at diagnosis [9].

In the present study, progressive advancing of clinical stages of breast cancer was positively correlated with progressive elevation of diabetes parameters (FBS, 2-hPPBS, HbA1c). Breast cancer women presented with stage-III disease had significantly higher BMI, FBS, 2-hPPBS, and HbA1c levels compared to women presented with stage-I disease. In addition, breast cancer women presented with invasive ductal carcinoma had significantly higher BMI, FBS, 2-hPPBS, and HbA1c levels compared to women presented with ductal carcinoma in situ. Consistently, breast cancer patients with diabetes were significantly more likely to present with advanced-stage cancer compared to women without diabetes, which may contribute to the higher mortality faced by breast cancer patients with diabetes [9].

Conclusion and recommendation:

In conclusion, type-2 DM is considered a risk factor for development of breast cancer. In addition, in type-2 diabetic women, breast cancer is often diagnosed at advanced stages and characterized by being of more aggressive pathologic subtype. Whether type-1 DM has similar effect on breast cancer was not evaluated in this study. Further studies are recommended to evaluate whether proper control of diabetic status to optimum targets could affect the progression of breast cancer and its response to therapy.

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