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Is There a Link Between Diabetes and Breast Cancer?

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ABSTRACT

Introduction: *Breast cancer is the most common of all cancers worldwide. It is rare among men of all ages and women less than 30 years. Incidence rates increase over a lifetime, slowing down around menopause. National Cancer Institute (NCI) in Egypt reported that breast cancer represents 35.1% of all female cancers. Both Diabetes and breast cancer are common chronic diseases in women. Nearly 16% of breast cancer patients have diabetes.* ***Aim:*** *This study was aiming to assess the level of CD44 and ILGF 1 in female patients with breast cancer with and without type II diabetes mellitus.* ***Patients and Methods:*** *53 Egyptian females with breast cancer had attended Minia Oncology Center. They were classified into 2 groups according to the presence of diabetes. Tissue CD44 and Tissue IGF-1 receptors expression, Estrogen Receptors, Progesterone Receptors expression were all estimated.* ***Results:*** *Egyptian females with breast cancer and diabetes had significantly higher IGF-1R and higher CD44 Expression and lower ER and PR Expression in malignant.* ***Conclusion:*** *The presence of diabetes mellitus may be an important contributor to breast cancer risk among Egyptian females. Both IGF-1R and/or CD44 over-expression associated with poor clinic-pathological outcomes of breast cancers among diabetic females.*

Keywords: Breast cancer, Diabetes, CD44, IGF1

INTRODUCTION

Breast cancer is the most common of all cancers worldwide, New cases of breast cancer diagnosed in 2012 were more than 1.4 million, it's responsible for nearly 700,000 deaths worldwide every year [1]. It is rare among men of all ages and women who are younger than 30 years. Incidence rates increase over a lifetime, slowing down around menopause [2]. There is very limited data as regards the prevalence and the incidence of breast cancer among Egyptian females; however, the National Cancer Institute (NCI) in Egypt reported that breast cancer represents 35.1% of all female cancers [3]. Diabetes mellitus is a global public health concern. 382 million people had diabetes in 2013 and this number is expected to rise to 592 million by 2035 [4]. In Egypt Diabetes is a fast-growing health problem with a significant impact on morbidity, mortality, and health care resources. The International Diabetes Federation IDF, (2019) listed that Egypt is one of the 19 countries in the number of patients with diabetes. IDF estimated that 8,222,600 individuals have diabetes with the prevalence of diabetes in adults 9.6% [5].

Diabetes and breast cancer are quite prevalent chronic diseases among women. Approximately 16% of breast cancer patients suffered from diabetes [6]. Women with diabetes had a 23% greater risk of subsequent breast cancer than those without diabetes [7]. Also, breast cancer patients who are diabetic have a 32% increased risk of chemotherapy-related complication and a 24%-61% increased risk of all causes of mortality compared to breast cancer patients without diabetes [8].

Aim of the Work

This study is aiming to assess the level of CD44 and ILGF 1 in female patients with breast cancer with and without type II diabetes mellitus.

PATIENTS AND METHODS

Fifty-three Egyptian females had attended the Minia oncology center. Their median age was 50 years (ranged from 35-70 years). All participants were informed about the aim of this study and were given written consent for their participation. The study was approved by the hospital's research ethics board. Patients were included if they are: Egyptian female, histologically confirmed breast cancer in all stages. Patients were excluded if previously or currently treated with chemotherapy or radiotherapy, have end-organ failure such as heart, liver, or renal failure. Women with a history or family history of any cancer or those previously taking contraceptive pills were also excluded. Patients were divided into 2 subgroups according to diabetes status: Group I included 28 non-diabetic Egyptian females with breast cancer. Group-II included 25 Egyptian females with breast cancer and type II DM. We used a comprehensive questionnaire to collect a complete: history in particularly menstrual, reproductive, menopausal, and diabetes status as well as family history of breast cancer and other cancers. BMI was calculated for all considering underweight as less than 18.5 kg/m, normal weight: 18:24, overweight: 25:29.5; obese: 30:35, and morbid obesity as more than 35 [9].

The waist circumference in centimeters was measured by standard measure tape applied to the waist at the level of the anterior superior iliac spine. Women with a waist circumference of ≤ 88 cm are considered normal [10].

The blood samples were collected after overnight fasting (about 8 hours). These samples were allowed to coagulate at room temperature for 10 minutes-20 minutes, centrifuged for 5 minutes at the speed of 2000 rpm-3000 rpm then the supernatant was removed, and plasma was separated and stored at -20°C until the following tests were conducted: Fasting blood glucose, serum creatinine, liver enzymes, and complete blood counts. The diagnosis of Diabetes Mellitus was done according to ADA, 2020 guidelines as a patient was considered diabetic if had any of the following criteria: FPG ≥ 126 mg/dl (7.0 mmol/L), or 2 h PG ≥ 200 mg/dl during an OGTT, Hb A1C ≥ 6.5% or random plasma glucose ≥ 200 mg/dl, in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. Breast cancer was confirmed by multiple breast tissue biopsies, while the staging of breast cancer was determined based on the TNM system which is based on definitions and recommendations of the European Society of Medical Oncology.

For both groups, multiple breast tissue biopsies were obtained from malignant breast and adjacent normal tissues then fixed and stained with immune-histochemical stain to assess: Estrogen Receptors expression, Progesterone Receptors expression, Tissue CD44 expression and Tissue IGF-1 receptor expression. The expression of CD44, and IGF-1, in malignant tissues, was categorized using the following four-point scale:

- 0 pointed to negative or <10% positive cells
- 1+ pointed to 10% to 50% positive cells with weak brawn staining
- 2+ pointed to >50% positive cells with weak brawn staining
- 3+ pointed to >50% positive cells with strong brawn staining 11

According to the final staining score for the expression of CD44: IHC 0 and 1+ were considered low expression and IHC 2+ and 3+ were considered a high expression

The expression of ER-α and ER-β were classified as follows:

- 0 pointed to <10% positive cells
- 1+ pointed to 10% to 50% positive cells with weak staining
- 2+ pointed to >50% to 80% positive cells with strong staining
- 3+ pointed to >80% positive cells with strong staining

Data were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) version 20.0. p-values less than 0.05 were considered statistically significant.

RESULTS

This study included 53 Egyptian females with a median age was 50 years old (ranged from 35-70) with biopsy-confirmed breast cancer, sub-grouped into two groups: Group-I had included 28 non-diabetic Egyptian females with breast cancer, group-II involved 25 Egyptian females with breast cancer and type II diabetes mellitus. Diabetic patients

presented with significantly older age (p=0.009), higher BMI (p=0.003), higher fasting blood sugar (p=0.001), larger tumor size (p=0.009), and greater number of LN metastasizes (p=0.006) higher probability for distant Metastasizes (p=0.003) compared with non-diabetic counterparts Table 1. Also, diabetic patients had significantly lower ER and PR Expression in malignant tissues (p-value=0.045 and 0.001 respectively) with significantly higher histological grading (p-value= 0.02) compared with non-diabetic patients. IGF-1R Expression in malignant tissues was significantly higher in diabetic versus non-diabetic patients (p=0.03) (Table 2). Malignant tissues had a significantly higher CD44 Expression in diabetic versus non-diabetic patients (p=0.028) (Table 3). Also, CD44 Expression in normal adipose tissues was significantly higher in diabetic versus non-diabetic groups (p=0.041) (Table 4). The study also revealed a significant Correlations between CD44 and IGF-1R in both malignant and normal breast tissues (p<0.001, 0.008, <0.001, and 0.004 respectively) among both diabetic and non-diabetic patients.

Table 1 Demographic and clinical data of a diabetic and non-diabetic group of patients

Statistics#	DM	N	Mean	Std D	p-value
Age (years)	Non-Diabetic	28	47.79	13.737	0.009*
	Diabetic	25	56.28	7.662	
BMI (kg/m^2)	Non-Diabetic	28	28.652	5.1228	0.003*
	Diabetic	25	32.537	3.8118	
F.B.S (mg/dl)	Non-Diabetic	28	95.39	12.218	0.001*
	Diabetic	25	215.96	49.302	
Tumor size (cm^2) (tumor surface area)	Non-Diabetic	28	8.321	6.695	0.008*
	Diabetic	25	13.132	7.3809	
LN Metastasis (No. of lymph nodes)	Non-Diabetic	28	10.57	10.189	0.006*
	Diabetic	25	18.84	9.254	
Distant Metastasis (%)	Non-Diabetic	28	8	-	0.001*
	Diabetic	25	14	-	
*: Statistically significant					

Table 2 Expression of IGF-1R in Normal and malignant breast tissues

	Tissues (a)	Mean ± SD	Mean Rank	Sum of Ranks	Z	p-value
IGF.1R Distribution (%) of positive cells throughout the slide	Normal	8.87 ± 14.6	30.82	1633.5	-7.7	0.001
	Malignant	62.4 ± 31.4	76.18	4037.5		

Table 3 Expression of CD44 among Normal and malignant breast tissues

	Expression	Normal tissue	Malignant tissue	p-value
		N=53	N=53	
CD 44	Low	35 (66%)	21 (39.6%)	0.006*
	High	18 (34%)	32 (60.4%)	

Table 4 Expression of CD44 findings among diabetic and non-diabetic patients

	DM	Expression		p-value
CD44 expression in normal tissue	Non-Diabetic (N=28)	Low	22 (78.6%)	0.041*
		High	6 (21.4%)	
	Diabetic (N=25)	Low	13 (52%)	
		High	12 (48%)	
CD44 expression in malignant tissue	Non-Diabetic (N=28)	Low	15 (53.6%	0.028*
		High	13 (46.4%)	
	Diabetic (N=25)	Low	6 (24%)	
		High	19 (76%)	

DISCUSSION

Breast cancers are the most common cancers affecting females worldwide, In Egypt, cancer breast represents 18.9% of total cancer cases (32.04% in women and 2.2% in men) with an age-adjusted rate of 49.6 per 100 000 population. 5-year survival about 97% in its early stage but it decreases to 20% once it metastasis to other body parts [11]. Type II diabetes mellitus and breast cancers are major causes of morbidity and mortality worldwide [6]. There is a 20% increased risk for breast cancer in patients with Type II diabetes mellitus. Diabetes also increases cancer mortality from 15% to 30% [12]. Moreover, 16% of patients with breast cancer suffered from diabetes [13]. Also, diabetes mellitus has been identified as an independent predictor of poor prognosis in patients with cancer breast [6].

The study was aiming to clarify the associations of Type II DM, CD44, and IGF 1R expression with clinic-pathological presentations of breast cancer among a sample of Egyptian females. This sample of Egyptian diabetic females with breast cancers had older age (mean=56.2 *vs.* 47.8), higher BMI (mean=32.5 *vs.* 28.65) compared with non-diabetic patients. These results were matched with Luo, et al. who also showed older age for diabetic women with cancer breast, (mean=71.9 y) compared with non-diabetic cancer breast patients [14]. Also, it is consistent with He, et al. who showed that patients with Type II DM with breast cancer were older [15]. With aging, there is a higher risk for the development of type II diabetes due to the combined effects of increasing insulin resistance and impaired pancreatic islet function. Age-related insulin resistance appears to be primarily associated with adiposity, physical inactivity, and sarcopenia [16].

Lorincz, et al. tried to explain the association between type II DM and postmenopausal breast cancers by the existence of metabolic syndrome which leads to hyper-insulinemia and overexpression of insulin receptors and Insulin-like Growth Factor (IGF-1) both act as mitogens [17]. Also presence of underlying obesity (as most type II DM patients are obese) results in hyperestrogenemia by peripheral aromatization of androgens in adipose tissue and Adipokines such as leptin, chemerin, and Adiponectin with their roles in the initiation and progression of breast cancer. The study showed that breast cancer patients with Type II DM were likely to be overweight or obese (BMI, ≥ 25 kg/m^2) compared with non-diabetic patients. Also, the current study showed that the diabetic females with breast cancers are presented with higher breast cancer TNM scoring, larger tumor size greater number of LN metastases, and a higher probability for distant metastasis when compared with non-diabetic patients. So the presence of diabetes was associated with more aggressive breast cancer. It also associated with negative ER, negative PR more than non-diabetic patients. Our results were matched with He, et al. who showed that Type II DM with breast Cancer had higher TNM staging, higher Lymph nodes involvement compared with non-diabetic patients [15]. Similar results were achieved also by Li, et al. as the majority of histological grade in diabetic patients with breast cancer, was II+III-class, Lymph node metastasis was more in breast cancer patients with diabetes [18]. Also, Srokowski, et al. demonstrated that a higher percentage of women with Type II DM and breast Cancer presented with a more advanced stage than non-diabetic one [8].

Similarly, Zhihua, et al. confirmed that patients with breast cancer and type II diabetes mellitus had more adverse outcomes throughout the full course of disease i.e., at the first presentation, throughout therapy, the pattern of recurrence finally cancer-related mortality [18]. These constellations of data reflect the poor prognostic effect of type II diabetes mellitus on outcomes of breast cancers. These data are in disagreement with Luo, et al. who found that the

presence of diabetes did not cause a statistically significant difference in tumor characteristics, including size, lymph nodes, grade, and estrogen and progesterone receptor status [19]. A probable explanation as these studies did not adjust for some confounding factors such as duration of DM, the difference in a regimen of therapy (insulin versus oral anti-diabetic medication), and intensive glycemic control versus less controlled diabetes, all must be taken into account to analyze the effect of diabetes on the prognosis of breast cancer.

IGF1 is the major mediator of the effects of the growth hormone; it thus has a strong influence on cell proliferation and differentiation and is a potent inhibitor of apoptosis. So IGF-I stimulation contributes to breast cancer progression through its mitogenic and antiapoptotic effects on the mammary epithelial cells.it also protects breast cancer cells from the toxic effects of radio- and chemotherapy [20].

The present study showed that there was a significant increase in the expression of IGF-1R in malignant breast tissues compared with normal breast tissues and more in diabetics than non-diabetics patients. This was in agreement with Xin, et al. who found similar results in cancer breast patients with diabetes [21]. Also, Yerushami, et al. showed that IGF-1R expression was higher in malignant cases compared to benign cases (46% *vs.* 15%) [22].

The increased expression of IGF-1 receptors was significantly associated with higher breast cancer TNM staging; larger tumor size, higher rate of LN metastasis, and distant metastasis. It also was significantly co-related with negativity for both ER and PR receptors. These results were in agreement with Bahhnassy, et al. who found that high levels of IGF-I were significantly associated with lymph nodes metastasis, distant metastasis, higher incidence of ER and PR receptors negativity [23]. Also, Al Sarakbi, et al. showed that the level of IGF-I mRNA expression was correlated to nodal metastasis and considered it as the best single prognostic indicator in human breast cancer [24]. Duggan, et al. identified IGF-1R overexpression as a marker of aggressive breast cancer and considered higher IGF-1R expression as independent predictors for poor overall survival and a higher rate of lymph nodes invasion [25]. Moreover, Alexandre Arcaro, concluded that inhibition of IGF-1R can be a potentially valuable target for breast cancer treatment [26]. In contrast Xin, et al. demonstrated that there was no correlation between IGF-1R expression clinic-pathological factors, such as the size of the tumor, lymph node metastasis, pathological type, ER, and PR status in the diabetic patient [21]. Also, Shin, et al. showed that Positive IGF-1R expression was associated with a positive hormone receptor status (for both ER and PR) [27].

CD44 is a marker of tumor-initiating cells, plays a role in tumorigenesis, and is linked to the progression of breast cancer CD44 was also reported to have an impact on the prognosis of breast cancer including recurrence and chemoresistance [28].

The study found that CD44 was significantly expressed in higher levels in malignant breast tissues compared with normal breast tissues (60.4% *vs.* 34%) with more levels in malignant breast tissues in diabetic patients compared with non-diabetic patients (76% *vs.* 46.4%). This was in agreement with Xu, et al. who found that the level of CD44 was higher in breast cancer tissues than in normal breast tissues [29].

This study explored that CD44 receptor expression was positively correlated with higher breast cancer TNM staging; larger tumor size, LN metastasis, and probability of distant cancer metastasis. Also, it was significantly correlated with higher histological grades of breast cancer, and higher incidence of ER, PR negativity in breast cancers. This was in agreement with Xu, et al. who found that CD44 protein abundance was greatly elevated in high-grade breast cancer tissues, and a higher level of CD44 was significantly correlated with lower status of ER and PR [29]. Similar results were confirmed by McFarlane, et al. who showed that Strong CD44 expression was associated with high-grade tumors, PR, ER negativity [30]. Klingbeil, et al. also reported that CD44 expression is associated with negative ER, PR [31]. These results signify that overexpression of CD44 receptors in malignant tissues linked to poorer prognosis in patients with breast cancers and diabetes mellitus. But Horiguchi, et al. had different results as higher CD44 expression was significantly correlated with smaller tumor size, negative axillary lymph node metastasis [32]. Also Natkshatri, et al. demonstrated that CD44 often correlates with a favorable prognosis in early noninvasive breast cancer, and indeed, CD44 may not function as a marker of tumor-initiating cells at this phase in breast cancer progression [33]. This inconsistency of results between these studies and our study could be explained by the variations in assessing CD44 mRNA expression might also contribute to heterogeneity methods and cutoff values used to assess CD44 expression were different [29].

CONCLUSION

The present study showed a significant positive correlation between CD44 and IGF-1R in both malignant and normal breast tissues among both diabetic and non-diabetic patients.

DECLARATIONS

Contribution Details

Royana Singh contributed to the conception, design, and writing of the study protocol and the design of search strategies; she located and obtained trial reports, helped to select and assess trials, conducted the data analysis, drafted and approved the final paper. Shubhrendu Shekhar Pandey contributed to the conception of the study protocol and the design of search strategies; he helped to locate and obtain trial reports and revised and approved the final paper. Ashish Ashish, Bhupendra Kumar helped to select and assess trials, contributed to the data analysis, revised and approved the final paper. All authors contributed to the conception, design, and writing of the study protocol conducted data analysis, and revised and approved the final paper.

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Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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