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ORIGINAL PAPER

Type 2 diabetes mellitus and prognosis in early stage breast cancer women

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Abstract It has been suggested that type 2 diabetes mellitus may affect breast cancer prognosis, possibly due to increased diabetes-related comorbidity, or direct effects of insulin resistance and/or hyperinsulinemia. The aim of this study was to determine the impact of diabetes on disease-free survival (DFS) following mastectomy for breast cancer patients. The cases included in this retrospective study were selected from breast cancer women who had undergone mastectomy and completed adjuvant chemotherapy from 1998 to 2010. Patients were classified into two groups: diabetic and non-diabetic. Patients' age, sex, menopausal status, body mass index (BMI), histopathological features, tumor size, lymph node involvement, hormone receptor and HER2-neu status, and treatment types were recorded. There were 483 breast cancer patients included in the study. Postmenopausal patients' rate (53.7% vs. 36.8%, $P = 0.016$) and mean BMI levels were statistically higher (32.2 vs. 27.9, $P = 0.007$) in diabetic patients. There was no statistical difference for histological subgroup, grade, ER and PR positivity, HER2-neu overexpression rate, and tumor size between the diabetic and non-diabetic group. Lymph node involvements were statistically higher in diabetic patients compared with non-diabetic patients ($P = 0.013$). Median disease-free survival is 81 months (95% CI, 61.6–100.4) in non-diabetic patients and 36 months (95% CI, 13.6–58.4) in diabetic patients ($P < 0.001$). The odds ratio of recurrence was significantly increased in those with HER2-neu overexpression and lymph node involvement and decreased with PR-positive tumors. Our results suggest that diabetes is an independent prognostic factor for breast cancer.

Keywords Type 2 diabetes mellitus · Breast cancer · Prognostic factor · Comorbidity

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Introduction

Breast cancer is the most common cancer (28%) and the second leading cause of cancer deaths (15%) among women [1]. Diabetes mellitus is also an important and growing health problem and affects about 7% of adults and 15% of people older than 60 years [2, 3]. In adults, type 2 diabetes mellitus accounts for about 90–95% of all diagnosed diabetes cases. Type 2 diabetes mellitus is characterized by insulin resistance and hyperinsulinemia. It has been shown that high levels of insulin are mitogenic for breast cancer cells [4, 5], and insulin receptors are often overexpressed in breast cancer [4, 6, 7]. Several studies and two meta-analyses have found that breast cancer risk in women with a history of diabetes mellitus is increased by 15–20% compared to women without diabetes mellitus. In addition, risk of all-cause mortality in diabetic breast

cancer patients is increased by 24–61% compared to breast cancer patients without diabetes [9, 10].

In general, studies on this subject have focused on the relationship between diabetes mellitus and increase in the incidence of breast cancer and risk of death. However, in the present study, we evaluated if there was a difference in demographic, histopathological, and survival characteristics between diabetic and non-diabetic patients.

Material and method

The cases included in this retrospective study were selected from patients who had undergone mastectomy and completed adjuvant chemotherapy (we have information about random glucose levels) stage I–IIIA breast cancer women from 1998 to 2010 at Medical Faculty of Dicle University. All patients were classified into two groups: diabetic and non-diabetic. Patients with history of type 2 diabetes mellitus or receiving treatment for diabetes mellitus (before breast cancer diagnosis) were assigned to the diabetic group and all the other patients with a normal glucose level were included in the non-diabetic group. Patients with history of type 2 diabetes mellitus after breast cancer diagnosis or type 1 diabetes mellitus and male breast cancer were excluded from the study. Positive staining for ER or PR was defined as the positive staining of more than 1%, and HER2 positivity was defined as 3(+) by an immunohistochemical (IHC) staining or HER2 gene amplification by fluorescence in situ hybridization (FISH). Patients' age, sex, menopausal status, body mass index (BMI), histopathological features, tumor size, lymph node involvement, hormone receptor and HER2-neu status, and treatment features were recorded.

DFS was analyzed for the whole follow-up period. DFS was calculated as the time from definitive surgery to local or distal relapse or death without relapse, or last follow-up (censored observations).

SPSS 11.5 software was used for statistical analysis. A univariate statistical analysis was performed with independent samples *t* test, Chi-square test, Fisher's test, Kaplan–Meier survival analysis, and log-rank test. A multivariate analysis was performed using Cox model. The parameters that identified as prognostic factor for breast cancer in previous studies were included in the model.

Results

We identified 986 breast cancer patients at Medical Faculty of Dicle University from 1998 to 2010. Of whom 789 patients were confirmed as undergone curative surgery. Two hundred and forty-six patients were excluded from the study because of unavailability of their glucose levels and/or clinical data. Thirteen patients with history of type 2 diabetes mellitus after breast cancer diagnosis or type 1 diabetes mellitus were excluded from the study. Ten male breast cancer patients were excluded from the study. Thirty-seven patients who had not completed their adjuvant chemotherapy were excluded from the study. Therefore, we included a total of 483 breast cancer patients into this study from the recorded case files. Of whom 54 (11.2%) were diabetic. Mean age was 48.2 ± 11.7 for all patients, 53.1 ± 11.2 for diabetic group and 47.6 ± 11.7 for non-diabetic group ($P = 0.001$). At baseline, postmenopausal subjects rate (53.7% vs. 36.8%, $P = 0.016$) and mean BMI levels were statistically higher (32.2 vs. 27.9, $P = 0.007$) in diabetic patient group (Table 1). There was no statistical difference in histological subgroup, grade, ER and PR positivity, HER2-neu overexpression rate, and tumor size between the two groups ($P > 0.05$, Table 1). Lymph node involvements were statistically higher in diabetic patients compared with non-diabetic patients (81.5% vs. 64.6%, $P = 0.013$, Table 1).

Differences were found between the two groups in treatment. Adjuvant radiotherapy application rate was similar in both groups (72.2% vs. 67.8%, $P = 0.453$). Anthracyclin containing regimen was the most common adjuvant chemotherapy strategy for diabetic (87.0%, $n = 47$) and non-diabetic patients (81.8%, $n = 351$). Taxane regimen was the second most common adjuvant chemotherapy strategy for diabetic patients (53.7%, $n = 29$) and a greater proportion of patients in this group used the drug compared with non-diabetic patient group (41.3%, $n = 177$, Table 1).

The median follow-up time was 32 months (range 6–192 months). Hundred and thirty-five patients suffered recurrence (28.2%) during the follow-up period. Distant metastasis was observed in 73.5% ($n = 100$) of these patients and local recurrence was observed in the rest (26.4%, $n = 35$). Median DFS was 81 months (95% CI, 61.6–100.4) in non-diabetic patients, and 36 months (95% CI, 13.6–58.4) in diabetic patients, and a statistically significant difference was observed between the two groups (Fig. 1, $P < 0.001$).

The odds ratio of recurrence was significantly increased in those with HER2-neu overexpression [odds ratio (OR), 2.04; 95% CI: 1.23–3.39, $P = 0.006$], lymph node (≥4 node) involvement (OR, 2.24; 95% CI: 1.07–4.71, $P = 0.034$), lymphovascular invasion (OR, 2.95; 95% CI: 1.49–5.88, $P = 0.002$) and presence of diabetes mellitus (OR, 2.21; 95% CI: 1.23–3.96, $P = 0.008$) and decreased with PR-positive tumors (OR, 0.57; 95% CI: 0.36–0.93, $P = 0.024$, Table 2).

Table 1 Characteristics of diabetic and non-diabetic breast cancer patients

Characteristics	With diabetes mellitus		Without diabetes mellitus		*P* value
	No	%	No	%	
Age (mean)	53.1 ± 11.2		48.2 ± 11.7		=0.001
BMI	32.2 ± 7.5		27.9 ± 5.5		=0.007
Menopausal status					=0.016
Postmenopausal	29	53.7	158	36.8	
Premenopausal	25	46.3	271	63.2	
Histologic subgroups ($n = 477$)					=0.490
Ductal	48	88.9	349	82.3	
Lobuler	2	3.7	42	9.9	
Others	4	7.4	33	7.8	
Grade ($n = 357$)					=0.431
Grade I	4	9.3	29	9.2	
Grade II	28	65.1	174	55.4	
Grade III	11	25.6	111	35.4	
ER status ($n = 421$)					=0.810
Positive	27	54.0	207	55.8	
Negative	23	46.0	164	44.2	
PR status ($n = 428$)					=0.978
Positive	30	58.8	221	58.6	
Negative	21	41.2	156	41.4	
HER 2 overexpression ($n = 406$)					=0.186
Positive	27	58.7	174	48.3	
Negative	19	41.3	186	51.7	
Tumor size					=0.817
<5 cm	44	81.5	355	82.8	
≥5 cm	12	18.5	74	17.2	
Lymph node involvement	44	81.5	277	64.6	=0.013
Adjuvant Radiotherapy	39	72.2	291	67.8	=0.462
Adjuvant Chemotherapy					
Taxane containing	29	53.7	177	41.3	=0.152
Anthracycline containing	47	87.0	351	81.8	=0.343

Discussion

This study demonstrated that diabetes mellitus is not only a risk factor for breast cancer development, but also an indicative of poor prognosis in breast cancer patients. In the literature, meta-analysis demonstrated that diabetes mellitus was associated with increased mortality rate in diabetic patients compared with non-diabetic cancer patients [9]. However, diabetic breast cancer patients have an increased risk of all-cause mortality [10, 11]. Although all-cause mortality was increased in diabetic breast cancer patients, the correlation between breast cancer-specific mortality and diabetes mellitus is not clear. Fleming et al. demonstrated that breast cancer-specific mortality was not increased in diabetic patients, whereas Srokowski et al. identified increased breast cancer-specific mortality in diabetic patients receiving chemotherapy [12, 13].

Besides its relationship with mortality, four studies examined the impact of diabetes mellitus on the stage of breast cancer [12, 14–16]. Three of four studies found a positive relationship between diabetes mellitus and the stage of breast cancer [12, 15, 16]. Studies on the relationship between tumor size, lymph node involvement and diabetes mellitus have produced conflicting results. Although a prospective study documented a strong relationship between tumor size, lymph node involvement and diabetes mellitus [12], an earlier retrospective study failed to show such a relationship [17]. In our study, we found a relationship between lymph node involvement and diabetes mellitus, but no relation between tumor size and diabetes mellitus. However, a relationship was found between diabetes mellitus and the risk of second primary contralateral breast cancer in a recent study [18]. All these data suggest that diabetes mellitus is an important risk factor for the

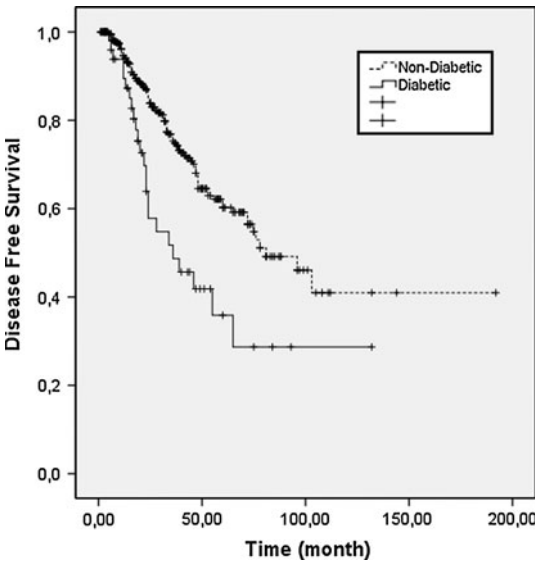

Fig. 1 Kaplan–Meier survival curve: survival following breast cancer stratified by diabetes status

Table 2 Cox regression analysis for disease-free survival in breast cancer patients

Parameter	OR	%95 CI	*P* value
HER-2 neu over expression	2.04	1.23–3.39	=0.008
Lymphovascular invasion	2.95	1.49–5.88	=0.002
Presence of diabetes	2.21	1.23–3.96	=0.008
≥4 lymph node involvement	2.24	1.07–4.71	=0.034
PR positivity	0.57	0.36–0.93	=0.024
Tumor size	1.33	0.75–2.37	>0.05
ER positivity	0.78	0.44–1.41	>0.05
Grade	1.21	0.70–2.07	>0.05
Age	1.01	0.98–1.042	>0.05
Menopausal status	0.56	0.26–1.22	>0.05

recurrence of breast cancer. In the present study, diabetes was found to be an independent prognostic factor for the recurrence of breast cancer patients.

It is clearly known that lymph node involvement is a poor prognostic factor in operated breast cancer patients. In the present study, there was a higher lymph node involvement in the diabetic group similar to previous studies [12]. A multivariate analysis was performed to eliminate this confounding factor as the association between presence of diabetes and poor prognosis can be attributed to it. As a result of analysis, presence of diabetes was considered to be an independent risk factor together with other prognostic factors. We observed that diabetic patients are more aggressively treated, which is most likely to be explained by the presence of more lymph node involvement in the diabetic group. In the literature, Srokowski et al. found that women with diabetes were less likely to receive taxanes compared with women without diabetes [12]. In our study, we have found that diabetic patients have received more taxane compared with the non-diabetic patients. However, our study has small patients number and including criteria of the study involving the completion of adjuvant treatment. Determining the presence of diabetes as an independent prognostic factor is an indication of a strong relationship although diabetic patients are more aggressively (taxane-containing regimen) treated.

As a result, studies investigating the relationship between breast cancer and diabetes mellitus combined with our results suggest that diabetes is an independent prognostic factor for breast cancer. Peairs et al. described three reasons to explain why diabetes is an independent risk factor. First, breast cancer may present with advanced disease during diagnosis as it was the case in our study. Second, the patients may be exposed to more chemotherapy-associated toxicity. And, finally, they may receive less aggressive therapy [11]. Of these reasons, the second and third ones did not pose a risk for our study because inclusion criteria required completion of the adjuvant therapy. Thus, diabetes being a poor independent prognostic factor in breast cancer can be explained by overexpression of insulin receptors in breast cancer [4, 6–8] and elevated insulin levels being mitogenic for breast cancer cells [4, 5]. In conclusion, based on these data, diabetic patients should be evaluated and treated considering that diabetes is an independent prognostic factor.

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