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Association between diabetes mellitus and adverse characteristics of breast cancer at presentation

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ABSTRACT

Type 2 diabetes mellitus is associated with increased incidence and inferior outcome of various malignancies. The aim of this study was to explore the impact of type 2 diabetes on breast cancer characteristics at presentation. The study population included 79 diabetic and 158 age-matched non-diabetic patients. Parity, country of birth, co-morbidity other than diabetes, and mode of diagnosis were similar in both groups. Mean body mass index (BMI) was higher among diabetic patients. Tumour stage and size were higher among diabetic patients and the differences remained significant after adjustment for BMI. Moreover, after adjustment for BMI, breast cancer among diabetic patients was more often hormone receptor negative. Our results show that diabetes mellitus is associated with negative prognostic factors at breast cancer presentation.

1. Introduction

Type 2 diabetes mellitus is a major health problem, affecting more than 6.5% of the adults and up to 15% of the elderly population in the United States.[1] Type 2 diabetes mellitus, which accounts for 95% of diabetes cases, is a high insulin state, caused by insulin resistance in fat and muscle tissues, which leads to increased production of insulin. β Cells could decompensate and low insulin levels may occur, but only in the late stages of the disease. The main risk factors for type 2 diabetes mellitus are genetic predisposition, older age and obesity.[2] Diabetes mellitus is associated with increased risk, as well as worse outcome, of various malignancies, including endometrial, colon and pancreatic cancers.[3–6]

Breast cancer is another common disease, affecting one of every eight women during her lifetime.[7] Up to 16% of older breast cancer patients also suffer from diabetes.[8] An association between type 2 diabetes mellitus and an increased risk of breast cancer has been suggested by some, but not all, studies.[9–11] We recently conducted a meta-analysis of published studies and found the association to be significant although modest.[12] Three mechanisms may operate in both diabetes mellitus and breast cancer: altered endogenous sex-hormone

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regulation, activation of the insulin-like growth factor (IGF) signalling pathway and activation of the insulin-signalling pathway.[2,12,13] Obesity, the major risk factor for type 2 diabetes, is also associated with significantly increased risk of breast cancer incidence, presumably due to activation of these three mechanisms.[14] In addition to the biological mechanisms connecting diabetes to breast cancer, diabetes has also been associated with inadequate use of screening mammography and administration of therapy not consistent with consensus guidelines.[15–17]

The association between diabetes mellitus and the clinical and pathological characteristics of breast cancer are currently unexplored. In this study, we have investigated the association between type 2 diabetes mellitus on the clinical and pathological characteristics of consecutive diabetic breast cancer patients who were treated at the oncology institute of Sheba Medical Center, Tel Aviv, Israel between 1999 and 2002.

2. Patients and methods

2.1. Study population

The study population included all consecutive type 2 diabetic female patients, newly diagnosed for invasive breast cancer, that were treated at the oncology institute of Sheba Medical Center, Tel Aviv, Israel between 01/1999 and 10/2002. If patients were not treated by insulin or oral hypoglycemic therapy, the diagnosis of type 2 diabetes mellitus was confirmed, according to the definitions of the American Diabetic Association, by the presence of fasting glucose levels of above 126 mg/dl in routine laboratory evaluation.[18] Each diabetic patient was matched to two non-diabetic female breast cancer patients who were diagnosed at the closest date of diagnosis with age ±2 years (control group). Patients were excluded from the study if they had a diagnosis of another concomitant malignancy or type 1 diabetes.

2.2. Data collection

Patients' charts were reviewed and clinical data, including age, country of origin, parity, family history of breast cancer, height and weight were collected, as well as diabetes diagnosis and treatment details. The charts were also reviewed for type of surgery, radiation therapy, hormonotherapy and chemotherapy. All pathology reports were reviewed for tumour histology, size, lymph node involvement, grade, and oestrogen receptor (ER), progesterone receptor (PR) and Her-2 status. Stage was defined according to the 1997 American Joint Committee on Cancer Staging System for Breast Cancer.[19] Body mass index (BMI) was calculated as weight (kg)/height^2 (m). Co-morbidity was evaluated by the Charlson's co-morbidity score, which consists of 19 parameters regarding major classes of diseases and functional impairments. The score is a simple, well-validated tool and is often used in the research of breast cancer.[20] Mode of diagnosis was categorized as screening (either by screening mammography or routine physical examination), or by symptoms (e.g., mass palpated by the patient, pain and nipple discharge).

2.3. Data and statistical analysis

The distribution of all categorical variables by study group was tabulated. 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. In the multivariate analysis, conditional logistic regression was performed to predict the influence of several variables on diabetes adjusting for BMI.

3. Results

3.1. Patients' characteristics

Of 1448 newly diagnosed breast cancer patients admitted during the study period, 79 diabetic breast cancer patients who met the study criteria were identified and matched to 158 non-diabetic breast cancer patients. The majority of the diabetic patients were treated by oral hypoglycemic agents ($n = 49$, 62%), and the rest by either diet ($n = 20$, 25%) or insulin ($n = 10$, 13%).

Patients' characteristics are presented in Table 1. The mean age at diagnosis was 64.9 ± 10 years for both groups, (range 31–90 years). Only 5% of the patients were younger than 50 years, and 15% were older than 75 years (data not shown). The groups were well balanced for country of origin, parity and family history of breast cancer among first-degree relatives. The crude co-morbidity score, as measured by the Charlson's co-morbidity score, was significantly higher among the diabetic patients ($P < 0.001$), but when adjusted for diabetes, the corrected score (excluding the category of diabetes mellitus) showed no difference between the groups. About half of the patients in both groups were diagnosed following the appearance of symptoms, mainly self-palpation of a breast mass, and only 26% were diagnosed following screening. As expected mean BMI was significantly higher (29.7 vs. 26.9, $P < 0.001$) among the diabetic compared to the non-diabetic patients.

3.2. The association between diabetes mellitus and breast cancer stage at diagnosis

Significant differences in the distribution of tumour stage were noticed between the study groups (Table 2). While almost half of the non-diabetic patients were diagnosed with stage I disease, only 24% of the diabetic patients were diagnosed at that stage (overall P value for differences in stage between the groups 0.002). Analysis of stage by early (T1/2, N0/1 and M0) versus advanced disease (T3/4, N2 or M1)[19,21] revealed that significantly more diabetic patients were diagnosed with advanced disease compared to the non-diabetic patients (18% vs. 8%, $P = 0.03$).

T stage was significantly higher among the diabetic patients, mainly due to differences in T1 and T2 disease (32% vs. 54% and 52% vs. 36%, respectively, overall $P = 0.028$). Compared to the non-diabetic patients, more diabetic patients had lymph node involvement, however, this difference was not statistically significant ($P = 0.32$). No differences were noticed