RESEARCH ARTICLE

Type 2 Diabetes Mellitus as a Risk Factor for Female Breast Cancer in the Population of Northern Pakistan

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Abstract

Background: There has been much research work in the past to ascertain the association between type 2 diabetes mellitus and breast cancer, but definitive evidence has been scanty. The present study was carried out to determine the association of type 2 diabetes mellitus with breast cancer in the female population of Northern Pakistan. Materials and Methods: This case-control study was carried out in the Oncology Department of NORI Hospital. A total of 400 patients were included. Data were entered into PSPP 0.8.1. Two-tailed significance tests were used and a p-value of 0.05 was considered significant. Results: There were a higher percentage of postmenopausal women in the diabetic breast cancer patients' group as compared to the non-diabetic subset. The odds ratio for the association between diabetes and risk of developing breast cancer was elevated with statistical significance (OR = 2.96; 95 % CI =1.3-6.3; p-value=0.004). The results of our study showed that diabetes is associated with a risk of developing breast cancer, especially in postmenopausal women (OR = 4.928; 95 % CI = 2.1-11.3; p-value=0.001). The association was particularly marked in obese subjects (OR = 31.49; 95 % CI = 1.8-536; p- value=0.01), as compared to non-obese subjects (OR = 0.642; 95 % CI = 0.2-1.7). Conclusions: Diabetes is strongly associated with obesity and it tends to increase the risk of breast Cancer, especially in postmenopausal women. A high-risk subset for breast cancer comprised postmenopausal, diabetic and overweight women.

Keywords: Breast cancer - diabetes - postmenopausal - obesity - Pakistan

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Introduction

Breast cancer is a major public health problem for women throughout the world. Type 2 diabetes has primarily been shown to increase the risk of breast cancer incidence (Larsson et al., 2007). Pakistan stands on number 6 among the top ten countries having increased burden of diabetes mellitus (WHO, 2003).

After menopause, the suprarenal glands and adipocytes are major estrogen sources. If body fat is excessive there is an increased hormonal bioavailability. The process of "androgen aromatization" is also responsible for the increased availability of estrogens in the body (McTernan et al., 2002). Also, the presence of hyperinsulinemia results in increased availability of Insulin-like Growth Factor I (IGF-I); which together with insulin could enhance migration and invasion of tumor cells (Macaulay, 1992; Sachdev and Yee, 2001). IGF-I signaling enhances estrogen receptor activation by inducing phosphorylation of the estrogen receptor, and IGF-I and estrogen have synergistic effects on the cell cycle signaling cascade and proliferation(Hamelers and Steenbergh, 2003). Because the IGF-I system can be cross-activated by insulin, the synergic effects of IGF-I and estrogen may also play a role in the etiology of Breast Cancer in the hyper-insulinemic state of type 2 diabetes (Chaudhuri, Chaudhuri and Patel, 1986; Guastamacchia et al., 2003). Experimental data suggests that type 2 diabetes enhances the process of carcinogenesis in breast; with IGF being one of the predominant factors (Novosyadlyy et al., 2010). It was confirmed in the Nurses' Health Study that the association of type 2 diabetes with the risk of developing Breast Cancer was higher in estrogen receptor positive tumors, since the concentration of estrogens in the body is a significant factor (Michels et al., 2003). High Body Mass Index (BMI) is also an established risk factor for the development of breast cancer in postmenopausal women (Carmichael, 2006).

Cancer patients from Northern Pakistan which include the twin cities of Rawalpindi, Islamabad, upper Punjab, Khyber Pakhtunkhwa, Gilgit-Baltistan, Kashmir, and Hazara attend NORI. This study was carried out to determine the association of type 2 diabetes mellitus with breast cancer in the female population of Northern Pakistan while the secondary end point was to assess the significance of other related factors and determine the subset with the highest risk of developing breast cancer in the presence of type 2 diabetes mellitus.

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Unfortunately however, there is still insufficient data regarding the effect of obesity and diabetes treatment on this association, even though these factors are associated with diabetes.

Materials and Methods

This case-control study was conducted in the Oncology Department of Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad, after review and approval by the Institutional Ethics Review Committee. Those female breast cancer patients were excluded who were below the age of 30 and above the age of 70 years and also no women were included as controls having a diagnosis of any type of cancer. There were 200 cases and 200 controls, making a total of 400 individuals, seen during the duration of the study. The data collection was completed from November 2014 to May 2015. Information obtained included history regarding age, menopausal status, the use of hormone replacement therapy or oral contraceptives, and physical activity, dietary fat intake, smoking history and diabetes status. Diabetes status was determined at the baseline, case–control interview. Participants were asked whether they had ever been diagnosed with diabetes. They were asked about medication use and whether the diabetes was controlled or uncontrolled. Patient data were recorded in the patient Proforma. Data were then transferred to PSPP software, for analysis. Risk of developing breast cancer was compared between participants with a self-reported diabetes diagnosis and those without a diabetes diagnosis and for this purpose chi-square test was employed. Two-tailed tests of statistical significance were used and the significance level was 0.05. For the purpose of evaluating this association, odds ratios (ORs) and 95 % confidence intervals (CI) were calculated. All models were adjusted for 10-year age group at diagnosis. Additional factors considered included: menopausal status and smoking history (Huqqa, cigarette, beerri). Use of hormonal birth control and hormone replacement therapy among postmenopausal women was considered as were the lifestyle factors (dietary fat, physical activity, and body size measured as body mass index). Mostly cases and controls belonged to the age group ranging from 40-49 years. For assessing the physical activity, the reference for intensity of physical activity was taken from Pacific Physical Activity Guidelines for Adults (Organization, 2008).

Results

There were 27 (17.69 %) breast cancer female patients in our study who reported having diabetes. There were a higher number of diabetic women with the postmenopausal status at diagnosis, as compared to the non-diabetics. There were no significant differences between those with and without diabetes with regard to smoking, use of hormonal replacement, oral contraceptives and tumor characteristics (ER/PR positivity).

The odds ratio for the association between diabetes and risk of developing breast cancer was elevated, and it was found to be statistically significant (OR=2.96; 95% CI =1.3-6.3; p-value=0.004). We found an association of diabetes with the risk of developing breast cancer among postmenopausal women, which was significant (OR=4.928; 95 % CI=2.1-11.3; p-value=0.001).

In our study, an increased association was detected among those who were obese (OR=31.49; 95 % CI=1.8-536; p-value=0.01), however those who had a BMI value of <30 had no significant association (OR=0.642; 95 % CI=0.2-1.7). Thus, higher values of BMI were related with increased association between diabetes and breast cancer development. We did not find any statistically significant associations among those who had high dietary fat intake (OR=1.509; 95 % CI=0.2-9.1; p-value=0.654). Among women who were engaged in low to moderate physical activity as compared to vigorous physical activity (OR= 4.56; 95 % CI=1.7-11.7; p-value=0.001), a statistically significant association was seen between diabetes and increased risk of breast cancer. However, the effect of

Table 1. Odds Ratio (95% CI) for the Development of Breast Cancer in Association with Diabetes, Grouped by Breast Cancer Risk Factors

	Diabetes		No diabetes				
	cases	controls	cases	controls	OR	95% CI	p-value
All subjects	27	10	173	190	2.96	1.3-6.3	0.004
Menopausal status							
Pre-menopausal	1	1	51	87	0.851	0.05-13.7	0.909
Post-menopausal	26	9	121	103	4.928	2.1-11.3	0.001
BMI (kg/m^2)							
<18.5 to <30	15	10	138	174	0.642	0.2-1.7	0.38
≥30	12	0	35	15	31.49	1.8-536	0.01
Physical activity							
Low/moderate	24	8	148	152	4.56	1.7-11.7	0.001
Vigorous	3	2	25	38	1.54	0.2-9.3	0.63
Smoking							
Smoker	1	0	6	9	3.25	0.1-80.3	0.47
Non smoker	26	10	167	181	3.9	1.1-13.8	0.03
Dietary fat intake							
Low/moderate	24	8	156	157	5.823	2.1-15.6	0.001
High	3	2	17	33	1.509	0.2-9.1	0.654
Hormonal replacement/birth control							
Yes	5	0	13	20	11.75	0.6-214.3	0.09
No	22	10	159	170	3.384	1.2-9.4	0.019

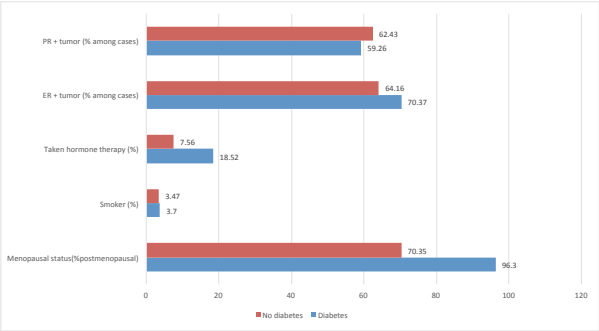

Figure 1. Selected Characteristics in Cases

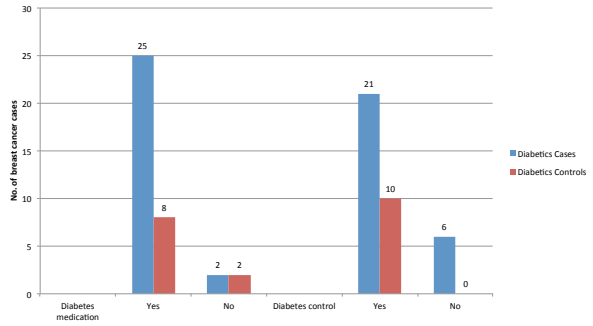

Figure 2. Effect of Medication use and glycemic Control on the Risk of Developing Breast Cancer

hormone replacement/birth control was not statistically significant (OR= 11.75; 95% CI= 0.6-214.3: p-value= 0.09). Also, there was no significant association of smoking with diabetes and breast cancer.

Among diabetics, there was no statistically significant association between diabetes medication use and the risk of developing breast cancer among cases. We also did not find any significant association between control of diabetes and breast cancer risk.

Discussion

Previous studies have also demonstrated the association between diabetes and increased risk of blood cancer. Unfortunately however, there is still insufficient data regarding the effect of obesity and diabetes treatment on this association, even though these factors are associated with diabetes. In our population based study, we found that diabetes was associated with risk of developing breast cancer among postmenopausal women and those with a higher Body mass index (BMI).

An international study studied the effect of diabetes on breast cancer incidence and mortality in the Long Island Breast Cancer Study Project, which included 1,447 breast cancer cases and 1,453 controls(Cleveland et al., 2012). Data for all-cause (n=395) and 5-year breast cancer-specific mortality (n=104) through December 2005 were determined for cases. Odds ratios (OR) and hazards ratios (HR) were determined by statistical analytical models. The results showed that diabetic women who were postmenopausal at diagnosis had an increased risk of developing breast cancer [OR=1.35; 95 % confidence interval (CI)=0.99–1.85]. These results are similar to those of our study which showed an even higher odds ratio (OR=4.928; 95 % CI=2.1-11.3; p-value=0.001). Their findings also suggested that diabetes may increase incidence of breast cancer in older women and non-whites, and mortality due to all causes. Our study also showed that diabetes increased the risk of breast cancer more so in postmenopausal women though we did not study the effect of diabetes on breast cancer related mortality or overall survival.

A similar case control study was conducted at NORI, Islamabad from January to July 2005 (Faheem et al., 2007). A total of 300 females, including 150 cases and 150 controls were

included in the study. Among the results, lack of breast-feeding (p≤0.001), low parity (p=0.001), history of smoking (p=0.001), postmenopausal status (p=0.002), a positive family history of breast cancer (p=0.006), unmarried status (p=0.008), and the use of contraceptive pills (p=0.03) were associated with breast cancer. These results are consistent with the findings of our study regarding postmenopausal status (p=0.001). However, we were unable to find a statistically significant association of smoking history (p=0.47) and hormonal birth control (p=0.09) with breast cancer.

However, no other studies have been conducted in our local setting regarding the association between diabetes and breast cancer risk.

High Body Mass Index is a well known risk factor for the development of breast cancer among postmenopausal women. We found an increased risk of breast cancer among women with a BMI ≥ 30 (OR=31.49; 95 % CI=1.8-536; p-value=0.01).

We also considered the other risk factors including obesity, low physical activity, use of foods high in fat content, and smoking etc. Other than low/moderate physical activity, other lifestyle and dietary factors showed no effect on the association. This is in conjunction with the existing body of evidence, where there still exists some controversy regarding the association of these factors with breast cancer. But low physical activity and obesity are risk factors for both Type 2 Diabetes and breast cancer. Since these factors are related to each other, it is difficult to separately evaluate the contribution of each of these on the diabetes-breast cancer association.

Our findings show that diabetes increases breast cancer risk in postmenopausal women. And since diabetes is on the rise in Pakistan, this could result in a considerable number of females who could be at risk of developing breast cancer. By better identifying such risk factors for breast cancer, it would be possible for the medical personnel to direct their attentions towards the prevention and control as well as effective screening of diabetes. This can be achieved by better coordination between diabetes and breast cancer treatments.

In conclusion, a history of diabetes has a significant association with obesity and this can result in an increased risk of breast cancer. A high-risk subset for breast cancer can be considered to comprise postmenopausal, diabetic and overweight women. These should be targeted for intervention.

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