RESEARCH ARTICLE

Diabetes Management

Implications of breast cancer with diabetes mellitus on patient outcomes and care

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Practice points

- The link between diabetes mellitus (DM) and breast cancer is of particular interest, given the common risk factors of obesity, diet and hyperinsulinemia.
- Previous studies typically have not examined how DM might affect breast cancer mortality or how breast cancer might alter outcomes of patients with DM in a single analysis.
- The purpose of this study was to examine whether breast cancer and its treatment affected glycemic control and therapy for DM and to assess its impact on short-term overall survival and time to recurrence.
- The presence of breast cancer and its treatment did not negatively affect metabolic control among patients with DM in this cohort.
- DM did not appear to affect either breast cancer OS or TTR in the short term.

ABSTRACT **Aims:** The aim of this study was to determine the impact of diabetes mellitus (DM) on short-term overall survival and time to recurrence (TTR) in breast cancer patients, and examine the impact of breast cancer on glycemic control in DM. **Methods:** From a data set of newly diagnosed breast cancer patients (2007–2011), we identified 109 patients with DM and 109 matched controls. **Results:** Hemoglobin A1c among cases did not significantly change over 1 year (p = 0.10). Cases and controls showed no differences in OS (hazard ratio: 1.25; 95% CI: 0.49–3.17) during the median follow-up of 2.2 years (range: 0.1–4.9 years) and no differences in TTR (hazard ratio: 1.00; 95% CI: 0.14–7.10). **Conclusion:** DM did not adversely affect metabolic control, short-term OS or TTR.

KEYWORDS
• breast cancer • diabetes mellitus • glycemic control • outcome • survival

Coexisting diabetes mellitus (DM) and cancer has been a topic of increasing interest [1]. DM is associated with an increased risk of development of many types of cancers [2–4]. Moreover, several studies have indicated that coexisting DM is associated with greater mortality in several types of cancers, including colorectal, endometrial, pancreas, liver and bladder [5,6]. A relationship between hyperglycemia and cancer mortality has also been noted [7,8].

The link between DM and breast cancer is of particular interest, given the common risk factors of obesity, diet and hyperinsulinemia [2–4]. Current hypotheses regarding mechanisms of the link between DM and breast cancer can be found in two recent reviews [2,5]. Postulated

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mechanisms include hyperinsulinemia, hyperglycemia, dyslipidemia, and chronic inflammation [2,5]. DM has been associated with a higher mortality rate among breast cancer patients. However, those studies examining the impact of DM on breast cancer mortality were population- or claims-based, and thus they often lacked or inconsistently accounted for many variables that could have confounded the results. For instance, some of these studies lacked detailed information on tumor grade or stage [5,9]. However, even in reports that contained detailed data on breast cancer characteristics [10–13], data on DM characteristics either were missing or were limited (e.g., presence of complications, timing of disease or medication usage were absent from the analyses). Statistical adjustment for some of these characteristics potentially could alter the interpretation of the interaction between DM and breast cancer.

Although the many studies have focused on how DM might affect breast cancer mortality, none have examined how breast cancer might alter outcomes of patients with DM. A new diagnosis of breast cancer does not make a patient with DM care less about managing the DM. Hence, in addition to wanting to know whether DM affects breast cancer outcome, we aimed to investigate how the diagnosis or treatment of breast cancer might affect metabolic control or the need to change hyperglycemia therapy in a patient with DM. Regardless of the outcome of such an analysis, knowledge about how these diseases interact have important implications for the future in how to plan for the more complex care of a patient with both diagnoses. Moreover, this information would help practitioners counsel patients on what to expect regarding how their breast cancer diagnosis and treatment might affect their DM care.

Our previous analysis characterized the prevalence of DM, the level of glycemic control, and the impact of DM on survival for several cancers in an academic general oncology practice [14]. That analysis showed no relationship between DM and breast cancer mortality; however, like many other reports, several cancer- and DM-related variables were not available [5–13]. Therefore, we revisited our previous cohort of breast cancer patients, this time collecting more detailed data on breast cancer and DM characteristics, to investigate whether DM affected overall survival (OS) and time to recurrence (TTR), and to examine whether breast cancer and its treatment affected glycemic control and therapy for DM.

Methods

• Overview of practice

The authors' institution is an established tertiary care academic medical center with a National Cancer Institute–accredited comprehensive cancer center that offers care for the full spectrum of solid and hematologic malignancies. Approximately 1600 cancer patients are evaluated annually in a multidisciplinary fashion that involves coordinated care and collaboration among physicians and researchers at our institution.

• Case selection

This retrospective, case–control study was approved by our institutional review board. Before data extraction, we obtained a listing of all patients with newly diagnosed breast cancer; patients were seen at our institution from 1 January 2007, through to 31 December 2011. Data also included age at diagnosis, date of diagnosis, and race and ethnicity. This initial data set was cross-referenced with a listing of all patients seen during the same period with an International Classification of Diseases, Ninth Revision, diagnostic code indicating DM. This allowed us to identify breast cancer patients with and without a DM diagnosis within the sampling time frame.

From this data set, we selected 123 patients with breast cancer and DM (cases) and 123 matched (1:1) patients with breast cancer but no DM (controls). Patients were matched using a greedy algorithm that minimized the weighted sum of the absolute differences in the matching variables between each case and all remaining possible controls [15]; the variables we matched (equal weighting) were: age at diagnosis of breast cancer within 5 years; race (white, black, Asian, American Indian, other/unknown); ethnicity (Hispanic, not Hispanic, unknown); and year of breast cancer diagnosis (2007–2010 vs 2011).

We retrieved glucose and HbA1c data for the study period from the laboratory information system. After this initial data set was developed, electronic medical records were reviewed for detailed information (e.g., timing of DM diagnosis, DM therapy, presence of DM complications and breast cancer therapy).

Chart review data were collected and managed using research electronic data capture tools

Table 1. Patient and disease characteristics at the time of breast cancer diagnosis (n = 218).

Characteristic	Without DM (n = 109)	With DM (n = 109)	p-value[†]
Age (median); range (years)	68 (28–91)w	68 (28–91)	NA
Race; n (%)			NA
– American Indian	3 (2.8)	3 (2.8)	
– Asian	3 (2.8)	3 (2.8)	
– Black	4 (3.7)	4 (3.7)	
– White	99 (90.8)	99 (90.8)	
Ethnicity; n (%)			NA
– Hispanic	4 (3.7)	4 (3.7)	
– Not hispanic	105 (96.3)	105 (96.3)	
Grade; n (%)			0.73
– 1	21 (20.6)	20 (19.6)	
– 2	56 (54.9)	50 (49.0)	
– 3	25 (24.5)	32 (31.4)	
– Unknown	7	7	
Stage; n(%)			0.66
– I	54 (52.4)	61 (59.8)	
– II	34 (33.0)	26 (25.5)	
– III–IV	15 (14.6)	15 (14.7)	
– Unknown	6	7	
BMI; median (range), kg/m^2[‡]	26.1 (19.0–51.7)	30.2 (17.8–57.1)	<0.001
Payer type; n (%)			0.34
– Insurance	38 (35.5)	33 (30.6)	
– Medicare	67 (62.6)	75 (69.4)	
– Self-pay	2 (1.9)	0 (0)	
– Unknown	2	1	
Alcohol use; n (%)			0.04
– No	38 (35.8)	53 (50.0)	
– Yes	68 (64.2)	53 (50.0)	
– Unknown	3	3	
Smoking status; n (%)			0.77
– Current	6 (5.6)	7 (6.6)	
– Former	52 (48.6)	47 (44.3)	
– Never	49 (45.8)	52 (49.1)	
– Unknown	2	3	
Employment status; n (%)	33 (38.4)		0.42
– Employed	47 (54.7)	26 (31.0)	
– Retired	6 (7.0)	53 (63.1)	
– Unemployed	23	5 (6.0)	
– Unknown		25	
ECOG performance status; n (%)	38 (69.1)	18 (54.5)	0.92
– 0	13 (23.6)	11 (33.3)	
– 1	4 (7.3)	4 (12.1)	
– 2–3	54	76	
– Unknown			
Steroid therapy; n (%)§			
– No	77 (73.3)	62 (76.5)	0.83
– Yes	28 (26.7)	19 (23.5)	
– Unknown	4	28	

[†]Patient groups were matched for age (within 5 years), race, and ethnicity.
[‡]Unknown value for two patients in each group.
[§]As therapy for breast cancer within the first year after breast cancer diagnosis.
DM: Diabetes mellitus; ECOG: Eastern Cooperative Oncology Group; NA: Not applicable.

Table 1. Patient and disease characteristics at the time of breast cancer diagnosis (n = 218) (cont.).

Characteristic	Without DM (n = 109)	With DM (n = 109)	p-value[†]
Chemotherapy; n (%)§			>0.99
– No	74 (72.5)	74 (73.3)	
– Yes	28 (27.5)	27 (26.7)	
– Unknown	7	8	
Hormonal therapy; n (%)§			>0.99
– No	29 (31.2)	29 (30.2)	
– Yes	64 (68.8)	67 (69.8)	
– Unknown	16	13	
Estrogen receptor status; n (%)			>0.99
– Negative	16 (15.1)	16 (14.8)	
– Positive	90 (84.9)	92 (85.2)	
– Unknown	3	1	
Progesterone receptor status; n (%)			0.64
– Negative	33 (31.1)	30 (28.0)	
– Positive	73 (68.9)	77 (72.0)	
– Unknown	3	2	
Her2/Neu status; n (%)			0.24
– Negative	93 (90.3)	87 (84.5)	
– Positive	10 (9.7)	16 (15.5)	
– Unknown	6	6	

[†]Patient groups were matched for age (within 5 years), race, and ethnicity.
[‡]Unknown value for two patients in each group.
[§]As therapy for breast cancer within the first year after breast cancer diagnosis.
DM: Diabetes mellitus; ECOG: Eastern Cooperative Oncology Group; NA: Not applicable.

hosted at our institution [16]. Research electronic data capture is a secure, web-based application designed to support data capture for research studies, providing: an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources.

• Statistical analysis

Statistical tests included paired t-tests for continuous variables, McNemar tests for binary variables, and Bowker tests of symmetry for categorical variables with more than two levels. HbA1c during the 1 year after breast cancer diagnosis was modeled within DM cases only (HbA1c was not available in most breast cancer patients without DM) using a linear mixed model containing a fixed effect for days since breast cancer diagnosis and an individual-specific random effect allowing each patient to have a different intercept. Glucose values during the 1 year after breast cancer diagnosis were modeled using a linear mixed model containing fixed effects for days since breast cancer diagnosis, case or control designation (i.e., grouping factor identifying whether the patient was in the DM or no-DM group), interaction between days and case–control designation, and individual-specific and matched pair-specific random effects.

OS was defined as time from breast cancer diagnosis until death from any cause, and patients were censored at the date last known alive if death was not documented. OS analysis included all 109 matched pairs. TTR was defined as time from breast cancer diagnosis until first recurrence, and patients were censored at the date of last disease evaluation if a first recurrence was not documented. Twelve patients were never disease free after the breast cancer diagnosis, so TTR analysis was restricted to the 97 matched pairs in which both patients were disease-free at some point after the breast cancer diagnosis. OS and TTR were estimated using the Kaplan–Meier method and compared between breast cancer patients with and without DM using Cox regression stratified by matched-pair designation.

Results

• Patient characteristics

Detailed chart reviews were conducted for all 246 patients originally selected. After the review,

14 case–control pairs were excluded from further statistical analysis for the following reasons: control patient did not have invasive breast cancer (n = 1), case patient did not have DM (n = 12), or both reasons (n = 1). Thus, the statistical analysis presented herein is based on 109 cases and 109 matched controls.

Table 1 summarizes characteristics of breast cancer patients with and without DM. No statistically significant differences in tumor characteristics (grade, stage, receptor positivity and Eastern Cooperative Oncology Group performance status) were detected. A similar number of breast cancer patients with and without DM received steroids, chemotherapy, or hormonal therapy during the first year of breast cancer treatment. The two cohorts were also well matched for sociodemographic characteristics (e.g., health insurance, smoking and employment status). The only differences between breast cancer patients with and without DM were that the patients with DM reported less use of alcohol (50% vs 64%; p = 0.04) and had greater BMI (median: 30.2 vs 26.1 kg/m^2; p < 0.001).

Characteristics of the breast cancer patients with DM (cases) are listed in **Table 2**. Most had Type 2 DM and the diagnosis of DM preceded that of breast cancer. The majority were being managed with oral hypoglycemic agents and did not have DM complications documented.

Table 2. Diabetes mellitus characteristics at the time of breast cancer diagnosis (n = 109).

Characteristic	Value
DM type; n (%)[†]	
– Type 1	13 (11.9)
– Type 2	96 (88.1)
DM diagnosis preceded breast cancer diagnosis; n (%)	
– No	9 (8.5)
– Yes	97 (91.5)
– Unknown[‡]	3
DM therapy; n (%)[†]	
– Diet	33 (30.3)
– Insulin	21 (19.3)
– Oral	48 (44.0)
– Oral + insulin	6 (5.5)
– Other[§]	1 (0.9)
Change in DM therapy within 1 year after breast cancer diagnosis; n (%)	
– No	76 (90.5)
– Yes	8 (9.5)
– Unknown[‡]	25
Started insulin within 1 year after breast cancer diagnosis; n (%)	
– No	62 (96.9)
– Yes	2 (3.1)
– Unknown[‡]	45
History of DM complications; n (%)	
– No	66 (77.6)
– Yes	19 (22.4)
– Unknown[‡]	24
DM complication within 1 year after breast cancer diagnosis; n (%)	
– No	66 (77.6)
– Yes	19 (22.4)
– Unknown[‡]	24
Type of DM complication; n (%)	
– Nephropathy	1 (0.9)
– Retinopathy	5 (4.6)
– Neuropathy	14 (12.8)
– Microalbuminuria	1 (0.9)

[†]At time of breast cancer diagnosis or at the initial DM diagnosis (only if it followed the breast cancer diagnosis).
[‡]No information noted in the medical record.
[§]DM in remission since weight loss after gastric bypass surgery.
DM: Diabetes mellitus.

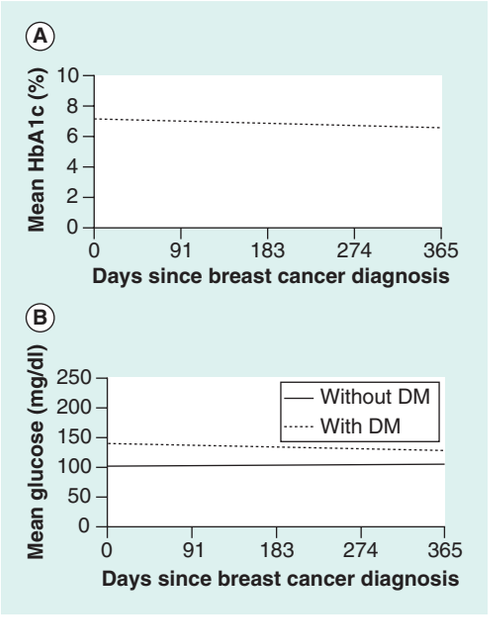

Figure 1. Estimated mean HbA1c and glucose in breast cancer patients with and without diabetes mellitus. Estimates were based on a mixed model. **(A)** HbA1c for cases (breast cancer with DM) only. **(B)** Glucose for both cases and controls (breast cancer without DM).
DM: Diabetes mellitus.

• Impact of breast cancer on DM metabolic control

HbA1c laboratory data were available in 70 breast cancer patients with DM. In total, 32 patients (46%) had one or more HbA1c measures of at least 7.0% within 1 year after breast cancer diagnosis. However, HbA1c levels did not significantly change over this first year (p =0 .10) (Figure 1A). Glucose laboratory data were available in 100 and 84 breast cancer patients with and without DM, respectively. Of the DM patients, 72 (72%) had one or more glucose readings of at least 125 mg/dl within 1 year after breast cancer diagnosis, whereas only 19 (23%) patients without DM had the same finding ($p < 0.001$). Glucose over the year following breast cancer diagnosis was significantly higher in patients with DM compared with patients without DM ($p < 0.001$), but it did not significantly change over time ($p = 0.83$), which was consistent between groups (interaction, $p = 0.21$) (Figure 1B).

• Changes in DM therapy

Within the DM group, 96 patients (88%) had Type 2 DM and 97 of 106 (92%; three unknown) had DM before breast cancer was diagnosed (Table 2). Initial DM therapy included diet (n = 33 [30%]), oral therapy (n = 48 [44%]), insulin (n = 21 [19%]), or oral therapy plus insulin (n = 6 [6%]). Eight patients required a change in DM therapy within 1 year after their breast cancer diagnosis. Two patients started insulin therapy after being on oral therapy alone. DM complications within 1 year after breast cancer diagnosis were reported for 19 patients; they included neuropathy (n = 14), retinopathy (n = 5), nephropathy (n = 1), and microalbuminuria (n = 1).

• Impact of DM on breast cancer OS & TTR

We observed no differences in OS between breast cancer patients with and without DM (hazard ratio: 1.25; 95% CI: 0.49–3.17) from the time of initial breast cancer diagnosis through a short median (range) follow-up of 2.2 (0.1–4.9) years (Figure 2A). Additionally, we observed no difference in TTR (HR: 1.00; 95% CI: 0.14–7.10) (Figure 2B). However, we note that very few patients died or had recurrence (22 and 6, respectively).

Discussion

As the prevalence of DM increases, it is increasingly likely to be a condition coexisting with other chronic diseases such as cancer. Before developing standards of care for patients with both of these complex diagnoses, patient profiles and how the two diseases interact and affect each other must be evaluated. Because breast cancer shares many risk factors with DM, we used it as a model to conduct a case–control study that included simultaneous characterization of breast cancer patients with and without DM to better define how DM affects breast cancer survival and also how breast cancer affects metabolic control in DM. Other than reported alcohol use and BMI, cases and controls were well matched.

This preliminary analysis incorporated multiple variables from breast cancer patients with and without DM. Such details included payer type, alcohol and tobacco use, employment status, Eastern Cooperative Oncology Group performance status, use of steroids, chemotherapy, or hormonal therapy, and estrogen receptor, progesterone receptor, Her2/neu status of the tumor, timing of DM diagnosis, mode of DM therapy and metabolic control.

The impact of breast cancer treatment (or any cancer treatment) on metabolic control in

DM has not been detailed. The presence of breast cancer and its treatment did not negatively affect metabolic control among patients with DM in this cohort. Only a few had DM therapy advanced to insulin, even though half the cases had HbA1c levels above currently recognized targets of control [17]. The use of steroids in only a minority of patients (only about a quarter of cases and controls) may have limited the impact of breast cancer therapy on hyperglycemia. Providers may have encouraged patients to be more attentive to monitoring and managing their DM, thus preempting any worsening glycemic control that might have occurred while receiving breast cancer therapy.

No record of glycemic monitoring was found in many of the patients' records. For instance, an HbA1c value was noted in only approximately 70% of cases. These patients possibly were being monitored elsewhere, so their glycemic control data would not have been included in this data set. Additionally, about half of cases with an available HbA1c did have values above 7.0%. Therefore, practitioners managing these cases should remind patients that follow-up for their DM is needed concurrently with their breast cancer care to assure that deterioration of glycemic control does not occur. Nonetheless, the observations here are encouraging for breast cancer patients with DM and the practitioners who care for them in that hyperglycemia did not worsen over the first year of breast cancer diagnosis and treatment. This observation by no means suggests that patients or their providers should not continue DM surveillance and management through appropriate monitoring, and changes in therapy should occur to maintain recommended metabolic targets. However, patients can be advised that, at least within the first year of breast cancer diagnosis, cancer therapy may not have a significant impact on metabolic control.

In this study, DM did not appear to affect either breast cancer OS or TTR over the short term. This is different from what is reported in much of the literature, which states that DM is associated with poorer survival [18–20]. We considered several explanations that might account for the differing observations of the current study. For instance, our analysis included only a short duration of follow-up. Differences in OS and TTR between cases and controls might emerge with longer observation. Alternatively, it may be that, even after carefully accounting for multiple important characteristics, there is no negative impact of DM on OS and TTR in breast cancer patients. Ongoing follow-up of this cohort is needed to establish the long-term impact of DM on breast cancer OS and TTR.

We acknowledge some limitations to this study. First, the study was performed retrospectively. Second, although cases and controls were well matched, the sample size was small because the time range, which dictated the availability of cases of newly diagnosed breast cancer with DM, was selected to reflect a modern cohort. The small sample size also precluded conducting multivariate modeling. Lastly, as indicated above, follow-up for OS, TTR, and metabolic control were not prolonged, and ongoing surveillance is warranted to determine if findings persist over time.

Despite the limitations, this is the first report (to our knowledge) to consider the reciprocal impact of breast cancer and DM in a single analysis. Although results are preliminary, the methodology described here can be used to examine similar questions about the interaction between DM and other types of cancers. These interactions may be unique for each type of cancer, and DM care may need to be individualized, depending on the nature of these interactions (e.g., some may require a higher

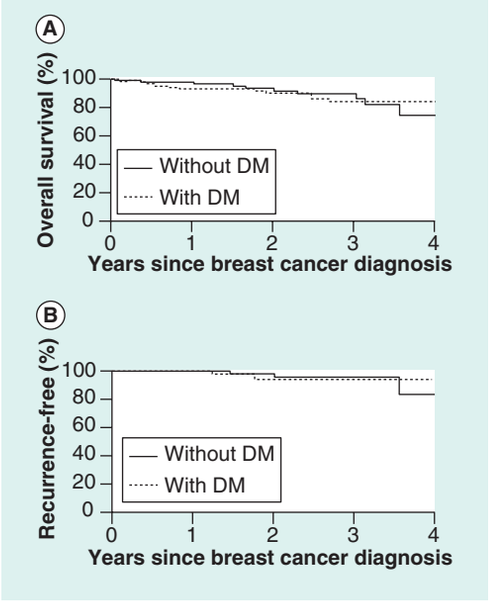

Figure 2. Kaplan–Meier plots of breast cancer patients with and without DM.(A) Overall survival. **(B)** Time to recurrence.
DM: Diabetes mellitus.

degree of monitoring, whereas others may not). Future study is needed so that adequate health care resources can be allocated to properly care for these patients with two complex diagnoses.

Future perspective

Health services research about patients who have cancer coexisting with DM is limited and the area is open for future study. For example, the additional health care cost imposed by diabetes on the patient with newly diagnosed breast cancer has not been evaluated but will be of interest when planning future allocation of health care resources. Another area in need of investigation is how quality of life among cancer patients is affected by diabetes. Further study of these patients will in turn lead to development of innovative care models and pathways for the patient population with diabetes and breast cancer and to testing such models in a randomized, controlled fashion.

Disclosure

This study was presented in poster format at the American Society of Clinical Oncology (ASCO) Breast Cancer Symposium, San Francisco, California, September 2013.

Financial & competing interests disclosure

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