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ORIGINAL REPORT

Clinically Defined Type 2 Diabetes Mellitus and Prognosis in Early-Stage Breast Cancer

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A B S T R A C T

Purpose
Self-reported diabetes has been associated with poor breast cancer outcomes. Research is needed to investigate the relationship between biologically determined glycemic control and breast cancer prognosis.

Methods
Archived baseline blood samples from the Women's Healthy Eating and Living Study were used to measure hemoglobin A1C (HbA1C) among 3,003 survivors of early-stage breast cancer (age of diagnosis, 28 to 70 years) observed for a median of 7.3 years for additional breast cancer events and 10.3 years for all-cause mortality. HbA1C levels provide an accurate, precise measure of chronic glycemic levels. Cox regression analysis was performed to assess whether baseline HbA1C levels predicted disease-free and overall survival.

Results
Only 5.8% of women had chronic hyperglycemia (defined as HbA1C levels $\geq$ 6.5%). Those with HbA1C $\geq$ 6.5% were older and more likely to be less educated, have nonwhite ethnicity, be obese, and have more advanced breast cancer at diagnosis. HbA1C was significantly associated with overall survival ($P_{trend} < .001$). After adjusting for confounders, risk of all-cause mortality was twice as high in women with HbA1C $\geq$ 7.0% compared with women with HbA1C less than 6.5% (hazard ratio [HR], 2.35; 95% CI, 1.56 to 3.54). For disease-free survival, there was a nonsignificant 30% increase in risk for HbA1C levels $\geq$ 7.0% (HR, 1.26; 95% CI, 0.78 to 2.02). During study follow-up, previously diagnosed rather than undiagnosed diabetes seemed to account for the increased risk.

Conclusion
Chronic hyperglycemia is statistically significantly associated with reduced overall survival in survivors of early-stage breast cancer. Further study of diabetes and its relationship to breast cancer outcomes is warranted.

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INTRODUCTION

Type 2 diabetes mellitus (hereafter referred to as diabetes) is increasing rapidly in the population at large, and studies suggest that 16% to 20% of women who have had breast cancer have diagnosed diabetes as a comorbidity.[1-3] Symptomless screening for diabetes is rare, and 30% of those with the disease may be undiagnosed.[4] Some research estimates that diabetes can remain undiagnosed for 5 to 10 years, and therefore, disease symptoms or complications may accompany the diagnosis.[5]

A number of studies have indicated that diabetes is associated with higher mortality in patients with breast cancer,[1-3,6,8-11] but it is unclear whether this is driven by a worse breast cancer prognosis or by competing risks such as cardiovascular disease. Recently, Patterson et al[12] reported that self-reported diabetes was associated with more than a two-fold increase in both breast cancer events and all-cause mortality. Whether the relationship between diabetes and breast cancer prognosis would be strengthened, reduced, or maintained when women with undiagnosed diabetes are included is unclear. It is also uncertain whether the additional mortality risk is specific to breast cancer or reflects the general higher mortality risk of diabetes.[13]

The hemoglobin A1C (HbA1C) assay is the test of choice for monitoring diabetes management because it provides a precise measure of chronic glycemic levels. Research indicates that HbA1C may also be used to diagnose diabetes because a cut point value of 7.0% is associated with increased risk of microvascular complications.[15] More recently, an International Expert Committee recommended the use of a cut point of 6.5% to definitively diagnose diabetes.[14] However, the Endocrine Society has published their reservations about this recommendation.[16]

In this secondary analysis, we explore the association of HbA1C levels and cut points with breast cancer progression. We measured HbA1C levels in archived blood samples of participants in the Women's Healthy Eating and Living (WHEL) Study, a multisite randomized trial that tested the effect of an intensive dietary intervention on new breast cancer events and survival. For study outcomes, we consider both breast cancer disease-free survival and overall survival.

METHODS

Participants

Between 1995 and 2000, the WHEL Study enrolled 3,088 women within 4 years of diagnosis of early-stage breast cancer (American Joint Committee on Cancer stage I [≥ 1 cm], II, or IIIA). Exclusions included the diagnosis of a comorbidity requiring a specific diet or the use of a medication that contraindicated a high-fiber diet and insulin dependence. After an average of 7.3 years of follow-up, breast cancer and vital status were confirmed on 96% of the original cohort. Details of the study have been reported previously.[17-18] Internal review boards at each site approved the study, and all participants provided written informed consent before enrolling.

Baseline Measures

Medical records pertaining to the initial cancer diagnosis were collected, and information on cancer characteristics and treatment was extracted and verified by an oncologist, including tumor stage and grade, tumor hormone receptor status, type of surgery, radiation, chemotherapy, and antiestrogen use. Weight and height were measured using standard procedures, and body mass index (BMI; weight in kilograms/height in meters squared) was calculated. Fasting blood was collected and separated using standard procedures and stored at −80°C. The study assessed demographics, self-reported menopausal status, and behavioral and lifestyle measures with standardized questionnaires. For this article, ethnicity was dichotomized into white/non-Hispanic and other (Hispanic/Latina, African American, Asian, Pacific Islander, and mixed/other).

Physical health, which was associated with prognosis in the WHEL Study,[19] was assessed using the well-validated 36-item Short Form health survey.[20] Following previous research, the physical health summary score was dichotomized as either low (bottom two quintiles) or moderate/high.[19] The frequency, duration, and intensity of physical activity were assessed using nine items from the Women's Health Initiative Personal Habits Questionnaire, which were validated in a subsample of WHEL participants[21] and converted into metabolic equivalent tasks as previously described.[22] A self-administered health status questionnaire queried a series of physician-identified comorbid conditions (including prediabetes and diabetes requiring or not requiring insulin) and medications including insulin and oral hypoglycemics (blood sugar–lowering pills).

HbA1C

HbA1C was measured in September 2009 using ion exchange high-performance liquid chromatography (D-10 System; Bio-Rad Laboratories, Hercules, CA) on archived samples of washed RBCs collected at the baseline clinic visit. Performance of the D-10 HbA1C methodology was assessed by inclusion of known quality control samples with high (10.0%) and low (5.8%) HbA1C levels; the coefficients of variation were 1.5% and 1.6%, respectively, for within-day runs and 1.9% and 1.9%, respectively, for between-day runs. Laboratory personnel performing these assays were blinded to study outcomes.

Assessment of Study Outcomes

The primary outcome was overall survival, which was defined as the time from study entry (on average, 2 years since diagnosis) to death from any cause. Throughout the study, information about hospitalizations or new breast cancer events was obtained by semiannual telephone interviews. Any reported event/death led to a medical record/death certificate review by two independent study physicians. Breast cancer event–free survival (disease-free survival) was defined as the time from date of enrollment to the development of a new breast cancer event (ie, locoregional or distant breast cancer or new primary tumor). Follow-up time was censored at the last documented staff contact date or at study completion (June 2006). Mortality data were updated through September 2009 using the Social Security Death Index. To measure accuracy of Social Security Death Index matching, sensitivity analyses were performed on censoring cut points and supported the chosen approach. Median follow-up time was 7.3 years for breast cancer event–free survival and 10.3 years for overall survival.

Statistical Analysis

Initial analyses included a simple plot of the proportion of study events by HbA1C value. Kaplan-Meier curves of overall survival and disease-free survival were calculated for the three HbA1C categories (< 6.5%, 6.5% to 6.9%, and ≥ 7.0%) with differences assessed statistically by the log-rank test. Univariate Cox proportional hazards models examined effects on disease-free and overall survival for each of the following: HbA1C, demographic variables (age, ethnicity, education level, and marital status), tumor characteristics (stage, grade, and receptor status), breast cancer treatment history (years since diagnosis, ever-use of antiestrogen, and treatment with radiation, chemotherapy, lumpectomy, and mastectomy), and other health measures (menopausal status [pre-, peri-, or postmenopausal], BMI, physical health, and physical activity level). We also examined the interaction terms between HbA1C and each of the covariates, none of which were statistically significant ($P > .05$). A backward elimination model omitted covariates that either had a $P > .05$ or changed the HbA1C hazard ratio (HR) by less than 10%. The variables of ethnicity, age, education, physical activity, and physical health were retained based on a priori assumption. The assumption of proportional hazards was checked for each model using plots of time-dependent coefficients estimated from Schoenfeld residuals. To explore how self-reported diabetes factored into the association between HbA1C and breast cancer events, the frequency of breast cancer events in each HbA1C category was counted and stratified by self-report diabetes status and use of blood sugar–lowering medication. All tests were two-tailed, and analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Variables Associated With HbA1C Level

HbA1C levels were measured on 97% of the study cohort (3,003 of 3,088 patients) and ranged from 4.2% to 13.9% (median, 5.6%). Most women (93.8%) had an HbA1C level less than 6.5%, 3.1% had a level of 6.5% to 6.9%, and 3% had a level ≥ 7% (Table 1). Participants with HbA1C levels ≥ 6.5% were on average 3.5 years older (SE, 0.65 year; $P < .001$), less likely to be college educated ($P < .05$), and more likely to be sedentary ($P < .01$) than participants with HbA1C less than 6.5%. White/non-Hispanic participants were less likely than other participants to have HbA1C levels ≥ 6.5% ($P < .001$). Other variables strongly associated with greater HbA1C category were higher BMI, poor physical health, and higher stage breast cancer (all $P < .001$).

Table 1. Participant Demographics and Clinical Characteristics by Baseline HbA1C in a Cohort of US Breast Cancer Survivors

| Characteristic | HbA1C | | | | | | P |
| | < 6.5% (n = 2,818) | | 6.5% to 6.9% (n = 94) | | ≥ 7.0% (n = 91) | | |
	No. of Participants	%	No. of Participants	%	No. of Participants	%	
Demographics							
Age, years							< .001
Mean	50.6		54.1*		53.7*		
SE	8.79		8.64		8.23		
Ethnicity/race							< .001
White, non-Hispanic	2,436	86.4	72	76.6	61	67.0	
Nonwhite	382	13.6	22	23.4	30	33.0	
College educated	1,545	54.8	44	46.8	40	44.4	.017
Married	1,989	71.1	57	62.0	59	65.6	.095
Breast cancer characteristics							
Cancer stage at diagnosis							< .001
I	1,109	39.4	33	35.1	25	27.8	
II	1,579	56.0	51	54.3	55	61.1	
IIIA	130	4.6	10	10.6	10	11.1	
Grade							.978
1	1,127	40.0	39	41.5	39	43.3	
2	1,018	36.1	31	33.0	29	32.2	
3	231	8.2	9	9.6	7	7.8	
Tumor receptor status							.336
ER positive/PR positive	1,733	62.9	62	66.7	56	62.9	
ER positive/PR negative	338	12.3	8	8.6	10	11.2	
ER negative/PR positive	119	4.3	1	1.1	7	7.9	
ER negative/PR negative	565	20.5	22	23.7	16	18.0	
Treatment							
Radiation	1,729	61.4	51	54.3	68	75.6	.008
Chemotherapy	1,963	69.7	65	69.2	63	70.0	.991
Lumpectomy	1,354	48.0	36	38.3	51	56.7	.044
Mastectomy	1,463	51.9	58	61.7	39	43.3	.044
Ever-use of antiestrogen	1,909	63.7	71	75.5	67	74.4	.128
Years since diagnosis							.901
Mean	2.0		2.0		2.0		
SE	1.04		1.04		0.97		
Other health measures							
Body mass index, kg/m^2							< .001
Mean	26.9		32.1*		34.2*†		
SE	5.70		7.51		8.58		
Obese (≥ 30 kg/m^2)	681	24.2	52	55.3	63	70.0	< .001
Poor physical health	1,169	41.5	51	54.3	56	62.2	< .001
Sedentary (< 150 MET-min/wk)	545	19.3	30	31.9	26	28.6	.001
Menopausal status							.026
Premenopausal	328	11.7	3	3.2	5	5.6	
Postmenopausal	2,230	79.3	85	90.4	77	85.6	
Perimenopausal	256	9.1	6	6.4	8	8.9	

Abbreviations: HbA1C, hemoglobin A1C; ER, estrogen receptor; PR, progesterone receptor; MET, metabolic equivalent.
*$P <$ .05 for comparison with HbA1C < 6.5% category.
†$P <$ .05 for comparison with HbA1C 6.5% to 6.9% category.

Additional Breast Cancer Events and All-Cause Mortality

As of June 2006, 503 participants had a breast cancer event over the median 7.3 years of follow-up (Table 2). The majority of events were distant recurrences (n = 344, 68%), followed by locoregional recurrences (n = 81, 16%) and new breast primary tumors (n = 78, 16%). As of September 2009, 414 deaths were recorded over a median follow-up time of 10.3 years. The majority of deaths were a result of breast cancer (n = 331, 80%), followed by other cancer (n = 41, 10%), other causes (n = 22, 5%), and heart disease (n = 11, 3%).

Unadjusted Analyses

Figure 1 shows the proportion of all-cause mortality for seven categories of HbA1C and displays a marked increase in events for women with HbA1C ≥ 7.0%, with 35% of women with HbA1C greater than 8.0% dying within the follow-up period. The unadjusted HR for continuous HbA1C (per one-unit increase) and overall survival was 1.29 (95% CI, 1.16 to 1.43). The Kaplan-Meier curve for overall survival displays a statistically significant association among the three HbA1C categories (Fig 2A). Compared with women with HbA1C of less than 6.5%, women with HbA1C of

Table 2. Association of Baseline HbA1C and Outcomes in a Cohort of US Breast Cancer Survivors Observed for a Median of 7.3 Years for Breast Cancer Events and a Median of 10.3 Years for All-Cause Mortality

	HbA1C					
	< 6.5% (n = 2,818)		6.5% to 6.9% (n = 94)		≥ 7.0% (n = 91)	
Outcome	No. of Participants	%	No. of Participants	%	No. of Participants	%
Breast cancer events (n = 503)	466	16.5	18	19.1*	19	20.9†
New primary tumor	73	2.6	3	3.2	2	2.2
Locoregional recurrence	75	2.7	3	3.2	3	3.3
Distant recurrence	318	11.3	12	12.8	14	15.6
All-cause mortality (n = 414)	368	13.1	18	19.1‡	28	30.8§‖
Breast cancer	307	10.9	11	11.7	13	14.4
Other cancer	34	1.2	3	3.2	4	4.4
Heart disease	5	0.2	2	2.1	4	4.4
Other	15	0.5	2	2.1	5	5.5
Unknown	7	0.2	0	0.0	2	2.2

Abbreviation: HbA1C, hemoglobin A1C.
*Comparison with HbA1C < 6.5% category, Cox model $P = .44$.
†Comparison with HbA1C < 6.5% category, Cox model $P = .15$.
‡Comparison with HbA1C < 6.5% category, Cox model $P = .05$.
§Comparison with HbA1C < 6.5% category, Cox model $P < .001$.
‖Comparison with HbA1C 6.5% to 6.9% category, Cox model $P = .04$.

6.5% to 6.9% and ≥ 7.0% were 60% (HR, 1.6; 95% CI, 1.00 to 2.57) and three times (HR, 3.01; 95% CI, 2.05 to 4.43) more likely to die during follow-up, respectively.

The unadjusted HR for continuous HbA1C (per one-unit increase) and disease-free survival was 1.00 (95% CI, 0.86 to 1.14). The Kaplan-Meier curve for breast cancer disease-free survival (Fig 2B) indicates that participants with an HbA1C ≥ 7.0% had a nonsignificantly higher event rate (40%) compared with women with HbA1C less than 6.5% (HR, 1.40; 95% CI, 0.88 to 2.21). The increase in risk across HbA1C categories was not statistically significant ($P = .11$).

Adjusted Analyses

After adjustment for stage, grade, age, ethnicity, education, physical activity, and physical health, the HR for continuous HbA1C (per one-unit increase) and overall survival was 1.20 (95% CI, 1.07 to 1.34). In the fully adjusted model, the risk of death for women with HbA1C of 6.5% to 6.9% was no longer statistically significant; however,
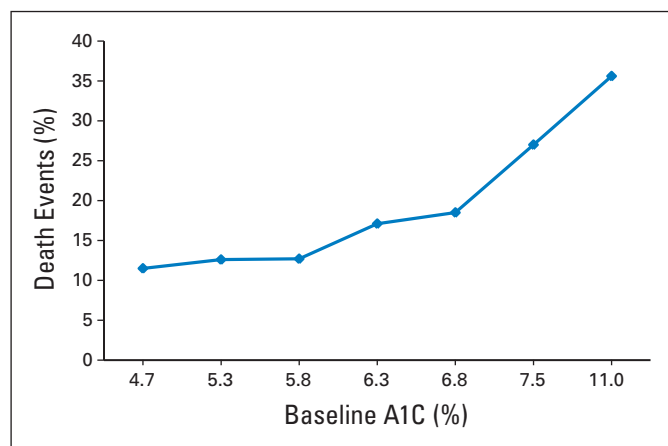
Fig 1. All-cause mortality events and baseline hemoglobin A1C (A1C) in a cohort of US breast cancer survivors with a median of 10.3 years of survival follow-up (N = 3,003).
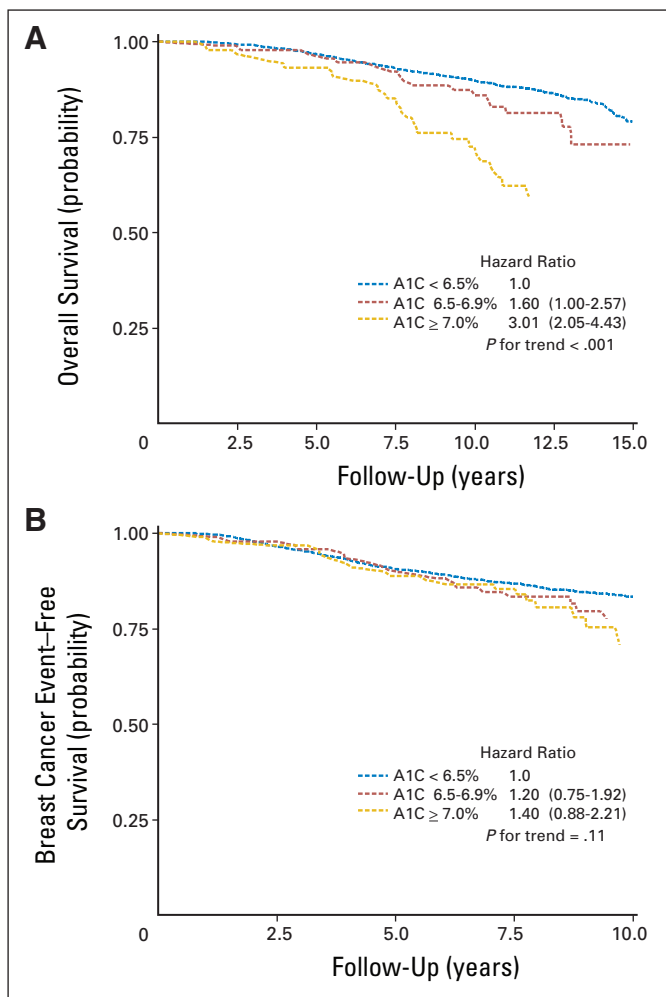
HbA1C ≥ 7% was associated with a 2.4-fold increase in risk (HR, 2.35; 95% CI, 1.56 to 3.54; Table 3). In models adjusting for the same covariates, neither continuous nor categorical HbA1C was significantly associated with risk of breast cancer recurrence (Table 3).

HbA1C Versus Self-Reported Diabetes in Relation to Breast Cancer Events

To investigate how undiagnosed diabetes factored into the association between HbA1C and breast cancer events, the distribution of breast cancer events by HbA1C category was stratified by self-report diabetes status. Of the 3% of participants with HbA1C ≥ 7.0%, less than half (37 of 91 participants) reported that they had diabetes on the baseline self-report questionnaire, and only 10% (nine of 94 participants) of the 3% of participants with HbA1C of 6.5% to 6.9% reported diabetes (Table 4). The majority of women (76.8%) who reported diabetes also indicated using blood sugar–lowering medication, and notably, these women had a two-fold higher rate of additional breast cancer events than women who did not report diabetes (32.6% v 15.6%, respectively). Of the 13 women who reported diabetes and no use of blood sugar–lowering medication, two experienced breast cancer events, and both had an HbA1C ≥ 7.0%; this computes to an incidence of 15.4%, which is nearly identical to the incidence of 15.6% found in women who did not report diabetes.

DISCUSSION

Compared with women with HbA1C less than 6.5%, women with HbA1C ≥ 7.0% had a statistically significant 2.4-fold greater risk of all-cause mortality during the median 10.3 years of follow-up. This association of higher HbA1C with worse overall survival was independent of age, race, BMI, cancer stage and grade, physical health, and physical activity and is similar in magnitude to previous WHEL Study findings using self-reported diabetes as the measure of exposure.[12] However, women with HbA1C ≥ 7.0% had a 26% higher rate of

Fig 2. Kaplan-Meier estimates of (A) overall survival with a median of 10.3 years of survival follow-up and (B) breast cancer event–free survival with a median of 7.3 years of follow-up according to baseline hemoglobin A1C (A1C) in a cohort of US breast cancer survivors (N = 3,003).

tions remain to be answered. Is there a threshold of glycemic status at which the risk for poor prognosis significantly increases? Is the increased mortality risk among breast cancer survivors with diabetes driven by an increase in cancer recurrence or a result of competing diabetes-related comorbidities such as cardiovascular disease? Findings in the present study suggest that HbA1C may be associated with breast cancer prognosis in a nonlinear fashion, that is, a threshold effect may exist in the diabetic range of HbA1C levels ≥ 7.0% and in individuals considered at high risk for diabetes (those who are obese and have a high HbA1C in addition to at least one other risk factor for diabetes). Eighty percent of the deaths in this study cohort were a result of breast cancer, and because of the much smaller number of non–breast cancer deaths, power was lacking to formally evaluate whether non–cancer-related deaths accounted for the statistically significant difference in overall survival time among the three HbA1C levels.

In this large study of breast cancer survivors, measured HbA1C more than doubled the number of women with diabetes compared with self-report identification; however, inclusion of these women with undiagnosed diabetes attenuated the previously identified diabetes association with additional breast cancer events.[12] Diagnosis of type 2 diabetes is most likely to occur in women experiencing symptoms. Therefore, it is likely that women with self-reported diabetes had longer disease duration and a history of worse glycemic control than women identified by HbA1C assays. Thus, our results could reflect the effect of severity and duration of diabetes on the risk of additional breast cancer events. Supporting this hypothesis, women who reported taking blood sugar–lowering medications for their diabetes (presumably reflective of more advanced disease) carried the highest risk of additional breast cancer events and mortality.

Diabetes may directly influence breast cancer progression and outcomes via several mechanisms including pathways mediated by high levels of insulin and insulin-like growth factors, sex hormones, and inflammatory markers. Both inflammation and obesity have biologic effects that could promote cancer, and the hyperinsulinemia that is associated with these conditions may itself augment cell proliferation and survival.[23-25] Clinical studies support this thesis. For example, Goodwin et al[26] reported that nondiabetic women whose fasting insulin levels were in the highest compared with lowest quartile were at a three-fold increased risk of death after breast cancer independent of BMI. Other studies using markers of insulin resistance, such as elevated waist-to-hip ratio[27] and presence of metabolic syndrome,[28] also found associations with a worse prognosis after breast cancer.

additional breast cancer events compared with women with HbA1C less than 6.5%, rather than the significant doubling of risk identified with self-reported diabetes.[12] Although a 26% increase in risk is clinically meaningful, this study did not have the power to detect an adjusted HR of 1.26 as statistically significant.

Despite the growing body of evidence that diabetes predicts a poor prognosis after a diagnosis of breast cancer, two important ques-

Table 3. Multivariate HRs of Overall Survival and Disease-Free Survival According to Baseline HbA1C in a Cohort of US Breast Cancer Survivors With a Median of 10.3 Years of Survival Follow-Up and a Median of 7.3 Years of Follow-Up for Additional Breast Cancer Events (N = 3,003)

HbA1C Category, %	No. of Patients	No. of Deaths	Overall Survival			No. of Breast Cancer Events	Disease-Free Survival		
			HR	95% CI	P		HR	95% CI	P
< 6.5	2,818	368	1.00*	—	—	466	1.00*	—	—
6.5-6.9	94	18	1.33	0.82 to 2.16	.25	18	1.11	0.69 to 1.80	.67
≥ 7.0	91	28	2.35	1.56 to 3.54	< .001	19	1.26	0.78 to 2.02	.34

NOTE. Analysis was adjusted for stage, grade, age, ethnicity, education, physical activity, and physical health.
Abbreviations: HR, hazard ratio; HbA1C, hemoglobin A1C.
*Reference category.

Table 4. Breast Cancer Events and HbA1C Stratified by Self-Reported Type 2 Diabetes Mellitus in a Cohort of US Breast Cancer Survivors (N = 3,088)

| | HbA1C | | | | | | | | | | | | Total Events | | |
| | < 6.5% (n = 2,818) | | | 6.5% to 6.9% (n = 94) | | | ≥ 7.0% (n = 91) | | | Missing HbA1C (n = 85) | | | | | |
Self-Report of Diabetes	No. of Participants	No. of Breast Cancer Events	%	No. of Participants	No. of Breast Cancer Events	%	No. of Participants	No. of Breast Cancer Events	%	No. of Participants	No. of Breast Cancer Events	%	No. of Participants	No. of Breast Cancer Events	%
No diabetes	2,287	353	15.4	71	14	19.7	47	7	14.9	76	17	18.4	2,481	391	15.6
Diabetes, no medication	5	0	0	2	0	0	6	2	33.3	0	0	0	13	2	15.3*
Diabetes, medication	4	2	50	7	2	28.6	31	10	32.2	1	0	0	43	14	32.6*
Missing†	522	109	21	14	2	14	7	0	0	8	1	12.5	551	112	20.3‡

Abbreviation: HbA1C, hemoglobin A1C.
*Because of small numbers, diabetes strata were combined (total events, n = 16/56, 28.6%; comparison with no diabetes, Cox model *P* = .01).
†Includes five women who completed the baseline health status questionnaire but did not complete question on diabetes.
‡Comparison with no diabetes, Cox model *P* = .65.

A diagnosis of diabetes may have indirect adverse effects on breast cancer outcomes by influencing medical decision making regarding breast cancer screening and management.[29] Studies have documented reduced breast cancer screening rates among diabetic women,[30] leading to later stage at diagnosis. Postmenopausal patients with breast cancer and diabetes frequently have one or more pre-existing comorbid conditions at diagnosis,[31] often leading clinicians to follow less aggressive cancer treatments[32-36] associated with lower survival rates.[2] We identified women with diabetes as more likely to have a later cancer stage at diagnosis and controlled for it in multivariate models but found no statistically significant differences in chemotherapy treatment or antiestrogen use.

Two other studies in addition to the earlier WHEL Study[12] found that the presence of comorbidities negatively affected breast cancer survival,[1,37] with diagnosed diabetes exerting a negative effect on survival independent of disease stage at cancer diagnosis.[1,37] Examining diabetes specifically, Lipscombe et al[9] conducted a population-based study evaluating the effect of diagnosed diabetes on breast cancer survival after adjusting for comorbidity. The study found that diabetes was associated with a nearly 40% increase in 5-year all-cause mortality, similar to that seen in diabetic women without breast cancer, suggesting that breast cancer survival is reduced in women with diabetes as a result of diabetes-related causes rather than direct effects of diabetes on cancer outcomes. In contrast, a study by Fleming et al[38] did not find diabetes to be a significant risk factor for increased mortality in patients with breast cancer. However, that study only examined 1-year mortality.

Diabetes is part of a cluster of problems, and the present study was unable to differentiate whether the effects observed were specific to HbA1C levels. Insulin dependence and diet restrictions were exclusion criteria for the WHEL Study, so our findings cannot be generalized to these subpopulations. Another subgroup with limited representation was women taking oral hypoglycemic medications; at baseline, the study had 43 such participants. Given the long natural history of recurrence in estrogen receptor–positive breast cancer, it would be important to examine the role of HbA1C in predicting late breast cancer events. At the completion of the main study in 2006, many participants did not reconsent for active follow-up. Thus, we limited reporting of additional breast cancer events to the average 7.3 years of the main study. However, we continued with passive follow-up for survival using the Social Security Death Index, thus strengthening the study with an additional 3 years of follow-up for this outcome. Additional strengths of this study include the reliable, accurate measurement of long-term glycemia with HbA1C assays, high rate of participant response, minimal missing blood samples, detailed and verified patient data on tumor and treatment characteristics extracted directly from medical records, and cancer events confirmed by two independent oncologists.

In summary, we found that chronic hyperglycemia, as indicated by elevated HbA1C levels, is independently associated with a statistically significant higher risk of all-cause mortality in breast cancer survivors. We also show evidence that a large percentage of breast cancer survivors who have diabetes do not know or do not report having diabetes. Of the women with HbA1C levels ≥ 7.0%, 60% did not report having diabetes, and even more striking, 90% of the women with HbA1C levels between 6.5% and 7.0% did not report having diabetes or prediabetes.

Diabetes, hyperglycemia, hyperinsulinemia, and associated metabolic disorders can be controlled and may present an opportunity for improving prognosis in early-stage breast cancer survivors. These data suggest that clinicians should consider measuring HbA1C in patients with breast cancer with symptoms of hyperglycemia or those at high risk for diabetes. These findings are hypothesis generating, and this association requires replication before HbA1C is routinely introduced into clinical practice. Nonetheless, randomized trials of interventions that target glycemic control in relation to both disease-free and overall survival end points may be warranted in this population.

AUTHOR CONTRIBUTIONS

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