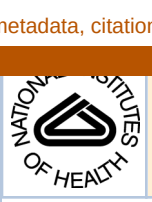

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The association of diabetes with breast cancer incidence and mortality in the Long Island Breast Cancer Study Project

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Abstract

Purpose—Diabetes has been associated with increased risk of breast cancer in a number of epidemiologic studies, but its effects on survival among women diagnosed with breast cancer have been examined less frequently. Importantly, prior investigations have rarely considered the influence of factors associated with diabetes such as obesity, age at diabetes diagnosis, duration of diabetes, or diabetes treatments.

Methods—We evaluated the effect of self-reported diabetes on breast cancer incidence and mortality in the Long Island Breast Cancer Study Project, which includes 1,447 breast cancer cases and 1,453 controls. Follow-up data for all-cause (n = 395) and 5-year breast cancer-specific mortality (n = 104) through December 2005 were determined for case women from the National Death Index. Adjusted logistic regression and Cox proportional hazards models were used to estimate odds ratios (OR) and hazards ratios (HR), respectively.

Results—Postmenopausal women with diabetes were at increased risk of developing breast cancer [OR = 1.35; 95 % confidence interval (CI) = 0.99–1.85], as were those who were not of white race regardless of menopausal status [OR = 3.89; 95 % CI = 1.66–9.11]. Among case women, diabetes was associated with a modestly increased risk of death from all causes [HR = 1.65; 95 % CI = 1.18–2.29], an association that was stronger in women who were obese at breast cancer diagnosis [HR = 2.49; 94 % CI = 1.58–3.93]. In analyses restricted to diabetics, there was no statistically significant effect of duration of diabetes or type of treatment on breast cancer incidence or mortality.

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Conflict of interest The authors declare they have no conflict of interest.

Conclusions—Our findings suggest that diabetes may increase incidence of breast cancer in older women and non-whites, and mortality due to all causes.

Keywords

Breast cancer; Diabetes; Survival

Introduction

Diabetes and breast cancer are increasing health concerns for women worldwide, particularly in older women [1]. Approximately 90–95 % of all cases of diabetes diagnosed are classified at type 2 diabetes (T2D), and it is currently estimated that over 10 % of women in the United States over the age of 20 have T2D, including those with undiagnosed disease [2]. T2D is characterized by insulin resistance and hyperinsulinemia, is associated with high BMI that is a well-established risk factor for breast cancer in postmenopausal women [3], and is associated with poor prognosis regardless of menopausal status [4, 5]. It is thought that T2D affects risk of developing breast cancer through the direct effects of insulin on breast tissue, or indirectly through the increase in sex steroids due to the inhibition of sex hormone-binding globulin (SHBG), increased insulin-like growth factor-I (IGF-I) production, and disruption of adipokines [6, 7]. These changes in circulating hormone levels can lead to abnormalities in cellular growth and regulation [8].

T2D has primarily been shown to increase the risk of breast cancer incidence, with a recent large meta-analysis reporting about a 20 % increase in risk for both case–control and cohort studies [9]. However, few population-based studies of survival after a breast cancer diagnosis have reported on this potentially important pathway [10–12] and even fewer have reported breast cancer-specific mortality [11, 13]. The biologic plausibility of an association with mortality is strong, as many components of diabetes have been linked to breast cancer incidence and prognosis including centralized obesity, insulin resistance, and raised fasting plasma glucose [6]. Furthermore, hyperinsulinemia has been associated with risk of recurrence and mortality in breast cancer [14].

For women with diabetes, the risk of developing or dying from breast cancer may also be affected by variations in the management of their diabetes, including types and length of treatments. There is encouraging evidence that metformin, an insulin sensitizer and the most commonly used therapy for patients with T2D, may decrease breast cancer risk by reducing hepatic glucose output [15]. Other treatments, however, such as insulin, or secretogogues, that stimulate insulin production, may increase cancer risk and death [16, 17]. There have been few studies that have investigated diabetes treatment on breast cancer risk [18, 19], and we are not aware of any studies that have investigated the influence of diabetes treatment in terms of survival.

Because diabetes is increasingly becoming a worldwide health problem where the number of women at risk is growing, it is important to understand the impact of diabetes and diabetes treatments on risk of developing breast cancer and survival after a breast cancer diagnosis. To investigate the effects of diabetes and diabetes treatments on risk of breast cancer and mortality, we conducted a large population-based study.

Materials and methods

This study draws upon data that were collected from participants as part of the Long Island Breast Cancer Study Project (LIBCSP), a population-based study of English-speaking residents of Nassau and Suffolk counties of Long Island, NY [20]. The study reported here

utilizes resources from both the case–control and the follow-up studies of the LIBCSP, as described below.

Study population

Case–control study—Eligible case participants were women newly diagnosed with a first, primary in situ or invasive breast cancer between August 1, 1996 and July 31, 1997. Cases were identified using a rapid reporting system established specifically for the LIBCSP and were confirmed by physicians' and medical records. The attending physician was contacted to confirm study eligibility and to seek permission to contact the patient. Controls were women who were residents of the same two counties, frequency matched by 5-year age group to the expected age distribution of cases. Potentially eligible control women were identified by Waksberg's method of random digit dialing (RDD) [21] for those under 65 years of age, and by Health Care Finance Administration (HCFA) rosters for those 65 years of age and older. Institutional review board (IRB) approval of the study protocol was obtained from each collaborating institution and participating hospital, and written informed consent was obtained from each participant prior to the baseline interview. A total of 1,508 women with breast cancer, of which 1,273 had invasive breast cancer, and 1,556 control women participated in the baseline case–control study interview. In the LIBCSP population, 93 % or participants reported their race as white, 4.8 % as black, and 2.2 % as other, which is consistent with the U.S. Census data for these two NY counties [20].

Follow-up study—The population-based cohort of women with breast cancer who participated in the baseline interview (n = 1,508) have been followed to determine complete first course of treatment for the first primary breast cancer diagnosis and vital status.

Data collection

Baseline, case–control data—Diabetes and most of the covariate data used in this analysis were collected as part of the LIBCSP baseline case–control interview, which for case women occurred about 2 months after the initial breast cancer diagnosis. The baseline structured questionnaire was administered in-home by a trained interviewer and took approximately 2 h to complete. Information obtained from the baseline questionnaire includes reproductive and menstrual history, exogenous hormone use (hormone replacement or oral contraceptives), family history of cancer, physical activity, smoking history, alcohol intake, demographic characteristics, and diabetes status. Descriptive characteristics for the entire LIBCSP study have been previously published [20]. As part of the baseline interview, a modified Block food frequency questionnaire was self-completed by 98 % of all LIBCSP respondents; these data were used to estimate intake of total fat and calories in the year prior to the baseline interview.

Additionally, as part of the baseline case–control study, medical records of the cases were abstracted for tumor stage, estrogen receptor (ER) status, progesterone receptor (PR) status, and initial course of treatment. Nearly two-thirds of the baseline interviews with cases occurred prior to the initiation of chemotherapy.

Diabetes status—Diabetes status was determined at the baseline, case–control interview. Participants were asked whether they had ever been told by a physician that they had diabetes, sugar diabetes, or high blood sugar. There were 7 participants (3 cases, 4 controls) with missing information on diabetes status. No distinction was indicated as to diabetes type, however, based on prior literature, in order to increase the probability that our population was limited to those with type 2 diabetes, women diagnosed with diabetes before the age of 30 were excluded from the analyses (n = 19) [22, 23], resulting in a total of 1,495 cases and 1,543 controls available for analysis. If the participant had reported having diabetes, they

were asked when they were diagnosed and were asked about medication use. Medication use was determined from the questionnaire where women responded to a question asking whether they had taken medication for diabetes for 3 or more consecutive months. Women reported the names of the medications used, and the duration they used each medication. Reports of using insulin, hepatic glucose production inhibitors (metformin), and/or an insulin secretogogue (majority of which were sulfonylureas, some were meglitinides) were classified as having used a medication.

Follow-up data among women with breast cancer—For women with breast cancer who participated in the LIBCSP baseline interview, follow-up telephone interviews were conducted in 2002–2004 by trained interviewers using a structured questionnaire with 1,098 case participants (of which 8 % were completed with a proxy). The follow-up interview included ascertainment of information on completed course of treatment for the first primary breast cancer diagnosis. These self-reported treatment data were compared with updated information from the medical records, which were retrieved as part of the follow-up and abstracted for 598 breast cancer cases. Trained abstractors reviewed medical records to determine the complete course of treatment for the first primary breast cancer diagnosis, and these data were compared with the respondent's self-reported treatment from the follow-up interview. A very high concordance was found between information abstracted from medical records and self-reported radiation therapy (Kappa = 0.97), chemotherapy, (Kappa = 0.96), and hormone therapy (Kappa = 0.92). Thus, self-reported breast cancer treatment was used for this analysis. At the time of the follow-up medical record review, nodal status for each woman's first primary breast cancer diagnosis was also ascertained.

Study outcome for the follow-up analyses—For the LIBCSP follow-up, the National Death Index (NDI) was used to ascertain all-cause and breast cancer-specific mortality among case participants. Cases were followed from diagnosis until December 31, 2005 for a mean of 96.4 months (range, 2.7–113.0). Among the 1,495 women in this study diagnosed with breast cancer, 303 (20.3 %) deaths occurred. Based on International Classification of Diseases (ICD) codes 174.9 and C-50.9 listed as a primary or secondary code on the death certificate, 106 (35.0 %) deaths after 5 years of follow-up were due to breast cancer.

Statistical methods

Risk of developing breast cancer and demographic factors were compared between participants with a self-reported diabetes diagnosis and those without a diabetes diagnosis using *t* tests and chi-square tests. All tests of statistical significance are two-sided and considered significant at the 0.05 level. All analyses were carried out using the statistical software package SAS version 9.2 (SAS Institute Inc., Cary, NC).

Case–control analyses—For the assessment of the association between the risk of developing breast cancer and a history of diabetes, odds ratios (ORs) and 95 % confidence intervals (CI) were calculated using unconditional logistic regression models [24]. All models were adjusted for 5-year age group at diagnosis. Additional factors considered as potential confounders included: variables related to demographic factors (race, income, education, marital status, religion), reproduction (parity, age at first live birth, breast feeding), and menstruation (age at menarche, menopausal status). Exogenous hormone use was also considered (hormonal birth control, hormone replacement among postmenopausal women) as was medical history (benign breast disease, family history of breast cancer), and lifestyle factors (alcohol consumption, dietary fat and total caloric intake, cigarette smoking, physical activity, and body size measured as body mass index [BMI; weight in kilograms divided by height in meters squared]). Using manual backward elimination, potential confounders were removed from models. Variables remained in the final models if their

exclusion changed the estimate of effect by ≥10 % [24]. Adjustment for most covariates did not alter the estimates of effect by more than 10 %, and therefore associations reported are only adjusted for 5-year age group, menopausal status (pre- vs. postmenopause), race (whites vs. blacks and others), and body size (BMI<30 vs. BMI ≥30). All case–control analyses were carried out on a dataset restricted to participants without missing values for menopausal status, race, or obesity resulting in a final dataset of 1,447 cases and 1,453 controls.

We also evaluated the effects of age at diabetes diagnosis, duration of diabetes, and diabetes medication use among those who reported having been diagnosed with diabetes. ORs and 95 % CI were calculated for the association between breast cancer and age at diabetes diagnosis (±55 years), median duration of diabetes (±7 years), whether they had ever received medication for diabetes for 3 or more consecutive months, and type of medication (insulin, metformin, secretogogues). Age at diabetes diagnosis and duration of diabetes were mutually adjusted for each other. Additionally, all types of diabetes medications we evaluated in the same model.

Effect measure modification on the multiplicative scale between categorical covariates was examined comparing the log likelihood statistic for logistic regression models with and without the cross-product terms [25]. We evaluated models stratified by age at breast cancer diagnosis (±65 years), menopausal status (pre- and postmenopause), BMI one year prior to breast cancer diagnosis (<25, ≥25–<30, ≥30), lifetime average physical activity (ever, never), lifetime average alcohol consumption (ever, never), median average daily caloric intake (±1,251.1 kcal/day), hormone replacement (ever, never), and race (white, black, other).

Survival analysis—Cox proportional hazards regression [25] was used to estimate hazard ratios (HR) and 95 % confidence intervals (CI) for all-cause and breast cancer-specific mortality in relation to a diabetes diagnosis reported at the time of baseline interview. Since most women who die as a result of their breast cancer diagnosis usually do so within 5 years, we presented only 5-year survival for breast cancer-specific deaths. Models re-run with follow-up time through 2005 were nearly identical to those limited to 5 years.

To investigate the differences in associations between diabetes and survival, analyses were stratified by selected covariates: age at breast cancer diagnosis (±65 years), menopausal status (pre- and postmenopause), BMI one year prior to breast cancer diagnosis (<25, ≥25–<30, ≥30), lifetime average physical activity (ever, never), lifetime average alcohol consumption (ever, never), median average daily caloric intake (±1,251.1 kcal/day), hormone replacement (ever, never), and race (white, black, other). Associations were also evaluated by stratification on the tumor characteristics, ER status (negative, positive), PR status (negative, positive), tumor stage (in situ, invasive), nodal status (node negative, node positive), and tumor size (<2 cm, ≥2 cm).

All models were adjusted for age at diagnosis. In addition to consideration of the covariates listed above for the case–control analyses, for the survival analyses, we also considered as potential confounders other factors including history of co-morbidities reported at the baseline interview (high cholesterol, history of blood clots, hypertension, previous myocardial infarction [MI], and stroke), tumor characteristics (tumor stage, tumor size, and nodal status), and treatment undergone for the original breast cancer diagnosis. Adjustment for most covariates did not alter the estimates of effect by more than 10 %, and therefore associations reported are adjusted for 5-year age group, menopausal status, race, body size, and MI only. All survival analyses were carried out on a dataset restricted to participants

with complete data for menopausal status, race, obesity, and MI resulting in a final dataset of 1,444 breast cancer cases.

Results

In Table 1, we report the distribution of characteristics of the LIBCSP stratified by self-reported diabetes from questionnaire data recorded in 1996–1997. There were 219 (7.2 %) participants in our population who reported having a diabetes diagnosis. Compared to non-diabetics, those with diabetes tended to be postmenopausal at diagnosis, have a higher BMI at diagnosis, and were less likely to engage in physical activity, drink alcohol or take hormone replacement than women without diabetes. Mean follow-up for women with breast cancer was 86.8 months for those with diabetes and 97.4 months for non-diabetics. There were no differences between those with and without diabetes according to tumor characteristics (ER/PR positivity, nodal status) or treatment type.

Case–control analysis

After adjustment for obesity, menopausal status, and race, the odds ratio for the association between diabetes and risk of developing breast cancer was slightly elevated, although not statistically significant (OR = 1.27; 95 % CI = 0.95–1.69) (Table 2). Estimates did not change appreciably with additional adjustment for other potential confounders such as physical activity, age at menarche, alcohol consumption, daily caloric intake, hormonal birth control, hormone replacement, education, or income (data not shown). We found a modest association of diabetes on the risk developing breast cancer among postmenopausal women, which was of borderline significance (OR = 1.35; 95 % CI = 0.99–1.85). The diabetes–breast cancer association was most pronounced when we limited the analysis to women over the age of 65 at breast cancer diagnosis (OR = 1.59; 95 % CI = 1.04–2.44).

When evaluating the potential effect measure modification of lifestyle factors on the association between diabetes and breast cancer, we found no association between those who were obese at diagnosis (OR = 0.99; 95 % CI = 0.65–1.53), whereas those who were not obese had an increased association (OR = 1.52; 95 % CI = 1.03–2.25). The diabetes–breast cancer associations were strengthened with decreasing BMI and were over twofold for those with a BMI between 18.5 and 25 at diagnosis (OR = 2.13; 95 % CI = 1.10–4.13) (*data not in table)*. Similarly, we saw stronger associations for those who gained less than 30 lbs since age 20 (OR = 1.72; 95 % CI = 0.92–3.20) and had either lost weight or gained less than 13.5 lbs after the age 50 (OR = 1.65; 95 % CI = 1.00–2.74; OR = 1.50; 95 % CI = 0.74–3.04, respectively; *data not in table*). We also observed increased associations among those who consumed fewer daily calories (OR = 1.66; 95 % CI = 1.10–2.52). Among women who did not engage in regular lifetime physical activity (OR = 1.60; 95 % CI = 0.99–2.59), we found that women with diabetes had increased risk of developing breast cancer, an association that approached statistical significance. We found no evidence of effect modification of the association between diabetes and breast cancer for use of postmenopausal hormones.

We observed modification of the effect of diabetes on breast cancer for race. After additional adjustment for both income and education, white women had no increased risk of developing breast cancer with diabetes; however, those of races other than white had over a threefold increase in the OR (OR = 3.89; 95 % CI = 1.66–9.11), but the estimate was unstable as reflected by the wide confidence intervals.

Survival analysis

Through 2005, there were 295 deaths overall and 148 deaths due to breast cancer, 104 of which occurred within 5 years of diagnosis. After adjusting for age, menopausal status, race,

obesity, and history of MI, women who reported having a diabetes diagnosis had increased all-cause mortality compared to women who did not have diabetes (HR = 1.65; 95 % CI = 1.18–2.29) (Table 3). This association was stronger among postmenopausal women. Additionally, women who were older age at diagnosis (≥65 years) also had higher mortality than those who were younger.

When stratified by body size, we found a higher risk of all-cause mortality in association with diabetes among those with a BMI of 30 or greater (HR = 2.49; 95 % CI = 1.58–3.93) than that seen in those with a BMI of less than 30 (HR = 1.20; 95 % CI = 0.73–1.99). Additionally, among women who were ever regular drinkers, although the association was not statistically significant, we found a stronger association for diabetes on breast cancer-specific mortality (HR = 2.14; 95 % CI = 0.90–4.69), whereas there was no increased risk of breast cancer death in association with diabetes among never drinkers.

Disease duration and medication use

Among diabetics, there was no consistent association between age at diabetes diagnosis, years since diabetes diagnosis, or diabetes medication use on the risk of developing breast cancer or mortality among cases (Table 4). After adjustment for duration of diabetes, modest non-significant increases in risk of developing breast cancer and all-cause mortality and diabetes were observed for women who were diagnosed with diabetes age after the age of 55 (OR = 1.71; 95 % CI = 0.71–4.11), as well as non-significantly increased all-cause mortality among those who took secretogogues (HR = 1.90; 95 % CI = 0.54–6.71). We also observed non-significant decreases in the association between diabetes and breast cancer risk and mortality among those who took metformin as treatment for their diabetes. We did not observe any associations for duration of diabetes, receiving treatment, or other treatment types.

Discussion

This large population-based study suggests a moderate and independently increased risk of all-cause mortality among women with a breast cancer diagnosis. After adjustment for menopausal status, race, obesity, and history of MI, breast cancer patients with diabetes had more than a 60 % increased risk of all-cause mortality than those without diabetes; this association was more than twofold for women with a BMI of 30 or greater at diagnosis. We also found that self-reported diabetes was associated with risk of developing breast cancer among older women and those with a lower BMI as well as those who had gained less weight during adulthood. In light of the fact that the prevalence of T2D is rapidly increasing, the results of our study have strong clinical implications for breast cancer prevention and improving survival.

Our findings of an 65 % increased risk of death due to any cause confirm those found in population-based studies that also show increased all-cause mortality after breast cancer diagnosis, finding excess deaths due to diabetes ranging from 35 to 76 % [11, 12, 26, 27]. Although all-cause mortality was significantly increased with diabetes, the association with mortality due to breast cancer specifically is less clear in our study. Some studies have found increased associations with breast cancer death [12, 28, 29]; however, other studies have not found this association [30]. It has been suggested that women with diabetes are less likely to receive mammography screening [31] and tend to present with more advanced disease at diagnosis [27]. However, in our study, we saw no difference in mammography use or tumor stage between women with and without diabetes. It is unclear why the association with all-cause mortality observed for diabetes is not seen for breast cancer-specific death. Some of the association could be due in part to medication use reducing insulin and other circulating hormone levels associated with breast cancer, as nearly three-quarters of diabetics in our

study regularly took medication for their condition. It is also possible that those with diabetes are more likely to die of other diseases that share the same risk factors as diabetes including renal disease, liver disease, and infections [32].

The risk of breast cancer in relation to T2D is thought to be due to increased circulating levels of insulin that are a direct result of insulin resistance. Biologic mechanisms of how diabetes can lead to breast cancer and affect prognosis include direct effects of high insulin levels, which have been shown to promote tumor proliferation, and insulin receptors are often overexpressed in breast cancer cells [33]. Insulin resistance can also indirectly affect breast cancer outcomes through increased sex steroid availability through decreases in sex hormone-binding globulin, increased IGF-I production, and disruption of adipokines [6]. In addition, T2D has been associated with chronic, low-grade inflammation. It has been shown that inflammatory molecules produced by adipose tissue as well as macrophages may lead to insulin resistance [34, 35].

As a result of the different mechanisms involved, medications taken for T2D may affect breast cancer depending on its mode of action, and there has been a recent effort toward studying how these medications affect cancer risk. Several studies have shown that medications that increase insulin levels, including use of insulin or insulin secretogogues, are associated with increased risk of cancer [16, 17, 36], while it has been suggested that treatment with insulin sensitizers, including metformin, may reduce risk of developing breast cancer and recurrence by killing the stem cells that are thought to be responsible for the spread of breast cancer [37]. We are not aware of any studies that have looked at medication use and survival after a breast cancer diagnosis; however, there is evidence that sensitizer medications, specifically metformin, may reduce cancer mortality [38]. While we were not able to adequately assess diabetes treatment on survival due to sparse data, there was a suggestion that metformin may reduce mortality and use of secretogogues increased mortality, although these associations may be biased due to unmeasured factors associated with medication compliance including regimen complexity, emotional factors, and medication cost [39]. Our results show no association with breast cancer development for any type of treatment, which are similar to those of another study, which looked at type of diabetes treatment and risk of developing breast cancer in women over the age of 65 [40], and the Nurses' Health Study that found no increased risk of breast cancer for diabetes among those taking diabetes medication [22]. A second study of Hispanic women found an increased risk of developing breast cancer with use of insulin using a control group consisting of women who had received a diagnostic mammogram due to either inconclusive or abnormal results [19]. A recent meta-analysis on metformin use also found no association with breast cancer [41]. Further research is needed to adequately assess the impact of types of diabetes treatments, including sulfonylureas for which there are no supporting data, on breast cancer outcomes.

Increased body size is an established risk factor for developing breast cancer in postmenopausal women and affects survival after breast cancer diagnosis [4, 42]. Increased body size is also a well-known risk factor for diabetes. Our estimates of association between diabetes and risk of developing breast cancer did not change with adjustment for obesity. However, while we found no increased risk of developing breast cancer overall in relation to diabetes, when we stratified this association by body size, we found an increased risk of developing breast cancer among women who with a BMI less than 30 (OR = 1.52, 95 % CI = 1.03–2.25); an association that was even stronger when restricted to those with a BMI<25 (OR = 2.13, 95 % CI = 1.11–4.10). The reasons for these observations are unclear. Perhaps women with increased body size are at increased risk of postmenopausal breast cancer due to factors associated with their obesity other than diabetes, such as elevated estrogen levels [43] and increased adipocytokines [44] that have been shown to increase breast cancer cell

proliferation and have involvement with angiogenesis. It is possible that women with lower BMI have fewer risk factors in general, and therefore their diabetes and hyperinsulinemia would have more of an impact on risk of developing breast cancer. Thus, it is possible that as is the case for exogenous hormone use, where effects are only evident among women without an increased body size [45, 46], the risk of breast cancer in association with diabetes is evident among women without an increased body size. Some researchers have attributed the interaction between body size and exogenous hormone use as a threshold effect; namely, the effects of hormone use are not evident among women with increased body size who are already estrogen-swamped [47]. Clearly, further research is warranted on modulating effects of body size on the association between diabetes and the risk of developing breast cancer.

We examined the association between diabetes and cancer while controlling for risk factors that are common to both, including age, obesity, physical activity, dietary factors, and alcohol consumption. Specifically, we assessed the association of diabetes and breast cancer with dietary factors often associated with diabetes such as high carbohydrate and high calorie intake. Our results do not suggest a difference in association when stratified by these factors. This is not surprising as the associations between these factors and breast cancer have been mixed [48–50]. However, low physical activity and obesity are strongly linked to both T2D and breast cancer. Because these factors are interrelated, it makes it difficult to identify the contribution of each on the relation of diabetes on breast cancer outcomes. Therefore, we cannot rule out residual confounding as an explanation for our findings.

We found more than a threefold increase in risk of developing breast cancer associated with diabetes among those of non-white race, although the number of non-white women in the LIBCSP is low and so cannot rule out chance for these findings. Because of the high prevalence of diabetes in African American communities, it is widely thought that race and ethnicity are major contributors to diabetes risk. More recent research, however, has shown that socioeconomic factors have a stronger association with prevalence of diabetes than race or ethnicity. Two recent studies report that after considering socioeconomic status, African Americans [51, 52] and Hispanics [51] have similar risks of diabetes as those found in Caucasians. In our study, however, after considering menopausal status, obesity, other comorbidities, income, and education, the association between diabetes and risk of developing breast cancer remained for non-whites. This may imply that diabetes has a differential effect on risk of developing breast cancer according to race or may simply imply that there is an additional unmeasured factor in our study that is driving the relationship. One reason for this association may be due to waist circumference (WC) that was not assessed in the LIBCSP. WC, a measure upper body obesity, correlates strongly with hyperinsulinemia [53] and is greater in African–American women than in white women with similar BMI [54]. Further research into this association including studies on environmental, behavioral, and genetic factors is needed.

There are a few limitations of this study that warrant mention. Although diabetes in our study was self-reported and did not distinguish between type 1 and type 2 diabetes, the majority of women who reported taking diabetes medications listed medications that are used to treat type 2 diabetes (85 %). Additionally, it is estimated that only 2.7 % of the population ages 20–44 has either undiagnosed or diagnosed diabetes [55]. Of the women in our study who reported having diabetes, 18 (7.8 %) women had a diabetes diagnosis before the age of 30, only 4 of whom were diagnosed before the age of 20. We excluded from analyses all women who reported having been diagnosed with diabetes before age 30 to increase the probability that the diabetes under investigation was adult-onset. However, we were not able to assess laboratory measurements that would confirm a diabetes diagnosis, nor were we able to adequately assess certain aspects of diabetes in relation to risk of

developing breast cancer, such as types and duration of therapies due to the low numbers of participants with diabetes reporting use of specific types of therapies.

Our findings show that diabetes increases breast cancer risk and mortality in older women, regardless of hormone receptor status of the tumor. This has strong clinical implications as the prevalence of diabetes in the United States continues to increase, which could result in a large number of women who could be at risk of excess death after a breast cancer diagnosis. Identification of factors that affect breast cancer risk and survival could help health care providers better counsel to their patients by offering screening for diabetes as well as developing interventions aimed at preventing T2D and better maintenance of diabetes, including coordination of diabetes and breast cancer treatments.

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Table 1

Selected characteristics of women diagnosed with a first primary breast cancer in 1996–1997, Long Island Breast Cancer Study Project, by diabetes status prior to diagnosis

Characteristics	Diabetes	No diabetes	*p* Value
Mean age (years)	63.6	57.4	<0.0001
Breast cancer diagnosis (%)	55.7	48.7	0.046
5-year death due to breast cancer (%among cases)	11.5	6.7	0.049
Menopausal status (%postmenopausal)	86.2	65.6	<0.0001
Race (% Caucasian)	84.9	93.4	<0.0001
BMI, mean	30.9	26.1	<0.0001
Energy intake (Kcal/day), mean	1,316	1,343	0.594
Regular physical activity (≥3 h/week) (%)	61.9	71.8	0.002
Ever regular alcohol drinker (%)	42.9	64.0	<0.0001
Ever take hormone replacement (%)	20.4	33.5	0.0003
Breast cancer stage (% invasive among cases)	87.7	84.1	0.287
ER + tumor (% among cases)	73.6	73.6	0.997
PR + tumor (% among cases)	66.7	64.0	0.619
Chemotherapy (% among cases)	33.9	41.9	0.239
Hormone therapy (% among cases)	72.2	60.6	0.089
Radiation therapy (% among cases)	50.0	61.7	0.081

Table 2

Odds ratios (95% CI) for developing breast cancer according to diabetes diagnosis, stratified by breast cancer risk factors among women diagnosed with breast cancer in 1996–1997, Long Island Breast Cancer Study Project

	Diabetes		No diabetes		OR[a]	95 % CI	OR[b]	95 % CI
	Cases	Controls	Cases	Controls				
All women	121	95	1,326	1,358	1.24	0.93–1.64	1.27	0.95–1.69
Menopausal status								
Premenopausal women	12	18	456	474	0.68	0.32–1.43	0.86	0.40–1.86
Postmenopausal women	109	77	870	884	1.40	1.03–1.91	1.35	0.99–1.85
Age at breast cancer diagnosis								
<65 years	50	58	895	968	0.93	0.63–1.38	1.03	0.69–1.55
≥65 years	71	37	431	390	1.74	1.14–2.64	1.59	1.04–2.44
BMI (kg/m^2)								
BMI >18.5 to <30	67	46	1,061	1,101	1.45	0.99–2.14	1.52	1.03–2.25
BMI ≥30	54	49	265	257	0.98	0.64–1.51	0.99	0.65–1.53
Ever regular lifetime physical activity[c]								
None	52	31	373	371	1.58	0.99–2.53	1.60	0.99–2.59
Any	68	64	946	983	1.06	0.74–1.51	1.09	0.75–1.56
Ever alcohol drinker								
Never drinker	69	48	495	515	1.47	1.00–2.18	1.41	0.94–2.09
Ever drinker	52	47	831	843	1.03	0.68–1.55	1.14	0.75–1.73
Average daily caloric intake[d]								
<1,275.1 kcal/day	69	39	665	666	1.67	1.10–2.51	1.66	1.10–2.52
≥1,275.1 kcal/day	43	50	630	651	0.85	0.55–1.30	0.89	0.58–1.38
Ever take hormone replacement[e]								
No	88	59	573	587	1.50	1.06–2.13	1.38	0.96–1.96
Yes	20	18	296	296	1.11	0.57–2.14	1.25	0.64–2.47
Race								
White	96	86	1,257	1,251	1.07	0.79–1.45	1.05	0.77–1.43
Other	24	9	103	66	3.14	1.25–7.87	3.89	1.66–9.11

[a]Adjusted for 5-year age group

[b] Additionally adjusted for menopausal status, race (white, other), and obesity (BMI <30, BMI ≥30)

[c] 12 missing responses for any lifetime physical activity

[d] 87 missing responses for average daily caloric intake

[e] Among postmenopausal women

Table 3

Hazard ratios (95 % CI) for all-cause mortality through 2005 and 5-year breast cancer mortality according to diabetes diagnosis, stratified by breast cancer risk factors among women diagnosed with breast cancer in 1996–1997, Long Island Breast Cancer Study Project

	All cause survival						Breast cancer 5-year survival					
	Diabetes		No diabetes		HR[a]	95 % CI	Diabetes		No diabetes		HR[a]	95 % CI
	Deaths	Total pop	Deaths	Total pop			Deaths	Total pop	Deaths	Total pop		
All women	49	121	246	1,326	1.65	1.18–2.29	14	121	90	1,326	1.17	0.63–2.19
Menopausal status												
Premenopausal women	4	12	63	456	1.30	0.43–3.89	3	12	32	457	1.76	0.48–6.49
Postmenopausal women	45	109	183	870	1.74	1.23–2.45	11	109	58	870	1.12	0.56–2.25
Age at breast cancer diagnosis												
<65 years	15	50	123	895	1.47	0.81–2.68	5	50	62	895	0.78	0.28–2.16
≥65 years	34	71	123	431	1.63	1.09–2.43	9	71	28	431	1.60	0.72–3.54
BMI (kg/m^2)												
BMI >18.5 to <30	19	67	186	1,060	1.20	0.73–1.99	7	67	64	1,060	1.49	0.64–3.48
BMI ≥30	30	54	60	263	2.49	1.58–3.93	7	54	26	263	1.22	0.51–2.91
Ever regular lifetime physical activity[b]												
None	24	52	96	373	1.55	0.95–2.53	8	52	36	373	1.22	0.51–2.88
Any	25	68	149	946	1.76	1.12–2.78	6	68	54	946	1.04	0.40–2.72
Ever regular alcohol drinker												
Never drinker	27	69	98	495	1.68	1.07–2.63	6	69	38	495	0.73	0.29–1.82
Ever drinker	22	52	148	831	1.61	0.98–2.64	8	52	52	831	2.14	0.90–5.10
Average daily caloric intake[c]												
<1,275.1 KCAL	26	69	118	665	1.60	1.01–2.53	4	69	42	665	0.73	0.24–2.15
≥1,275.1 KCAL	18	43	119	630	1.81	1.07–3.08	8	43	45	630	2.05	0.89–4.69
Ever take hormone replacement[d]												
No	38	88	141	586	1.70	1.17–2.48	9	88	46	586	1.05	0.49–2.24
Yes	6	20	45	299	1.86	0.77–4.50	1	20	12	299	1.01	0.13–7.92
Estrogen–Progesterone Receptor Status[e]												
ER−PR−	12	17	54	187	1.53	0.76–3.10	5	17	32	187	0.79	0.27–2.31
ER−PR + breast cancer	2	6	13	44	0.69	0.11–4.22	1	6	4	44	0.32	0.01–12.5

	All cause survival						Breast cancer 5-year survival					
	Diabetes		No diabetes		HR[a]	95 % CI	Diabetes		No diabetes		HR[a]	95 % CI
	Deaths	Total pop	Deaths	Total pop			Deaths	Total pop	Deaths	Total pop		
ER + PR− breast cancer	5	12	33	127	2.33	0.83–6.55	2	12	14	127	1.82	0.36–9.25
ER + PR+	21	52	87	510	1.70	1.02–2.85	4	52	22	510	1.32	0.41–4.24
Estrogen Receptor Status[e]												
ER−	14	23	67	231	1.48	0.79–2.77	6	23	36	231	0.83	0.32–2.14
ER+	26	64	120	637	1.74	1.11–2.74	6	64	36	637	1.44	0.56–3.67)
Progesterone Receptor Status[e]												
PR−	17	29	87	314	1.93	1.10–3.37	7	29	46	314	1.25	0.54–2.93
PR+	23	58	100	554	1.64	1.01–2.85	5	58	26	554	1.35	0.48–3.81

[a]Adjusted for menopausal status, race (white, other), obesity (BMI <30, BMI ≥30), and history of myocardial infarction

[b]8 missing responses for any lifetime physical activity

[c]40 missing responses for average daily caloric intake

[d]Among postmenopausal women

[e]Not all breast cancer cases had data for receptor status (n = 955 with receptor status)

Table 4

Odds ratios (95 % CI) and hazard ratios (95 % CI) for the associations of select diabetes characteristics and breast cancer risk and overall survival among diabetic women, Long Island Breast Cancer Study Project, 1996–1997

Characteristics	Controls	Cases	Deaths	OR[a]	95 % CI	Overall death HR[b]	95 % CI
Age at diabetes diagnosis[c]							
<55 years	50	45	15	1.00		1.00	
≥55 years	38	56	31	1.71	0.71–4.11	1.74	0.67–4.54
Duration of diabetes[d]							
<7 years	45	42	19	1.00		1.00	
≥7 years	43	59	27	1.70	0.81–3.57	1.31	0.61–2.83
Received treatment							
No	23	31	8	1.00		1.00	
Yes	65	70	29	0.67	0.34–1.34	1.43	0.62–3.28
Types of treatment[e]							
No insulin	49	50	21	1.00		1.00	
Took insulin	16	20	8	1.15	0.40–3.40	0.91	0.29–2.82
No metformin	47	57	25	1.00		1.00	
Took metformin	18	13	4	0.68	0.28–1.66	0.53	0.16–1.82
No secretogogue	14	15	4	1.00		1.00	
Took secretogogues[f]	51	55	25	1.29	0.42–3.99	1.90	0.54–6.71

[a] Adjusted for menopausal status, obesity, and race

[b] Adjusted for menopausal status, obesity, race, and history of BMI

[c] Additionally adjusted for duration of diabetes

[d] Additionally adjusted for age at diabetes diagnosis

[e] Any treatment versus no treatment; mutually adjusted for other treatments

[f] Majority of secretogogues were sulfonylureas