Association of Obesity and Diabetes With the Incidence of Breast Cancer in Louisiana

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Introduction: Breast cancer is a heterogeneous disease, consisting of multiple molecular subtypes. Obesity has been associated with an increased risk for postmenopausal breast cancer, but few studies have examined breast cancer subtypes separately. Obesity is often complicated by type 2 diabetes, but the possible association of diabetes with specific breast cancer subtypes remains poorly understood.

Methods: In this retrospective case-control study, Louisiana Tumor Registry records of primary invasive breast cancer diagnosed in 2010−2015 were linked to electronic health records in the Louisiana Public Health Institute's Research Action for Health Network. Controls were selected from Research Action for Health Network and matched to cases by age and race. Conditional logistic regression was used to identify metabolic risk factors. Data analysis was conducted in 2020−2021.

Results: There was a significant association between diabetes and breast cancer for Luminal A, Triple-Negative Breast Cancer, and human epidermal growth factor 2−positive subtypes. In multiple logistic regression, including both obesity status and diabetes as independent risk factors, Luminal A breast cancer was also associated with overweight status. Diabetes was associated with increased risk for Luminal A and Triple-Negative Breast Cancer in subgroup analyses, including women aged ≥50 years, Black women, and White women.

Conclusions: Although research has identified obesity and diabetes as risk factors for breast cancer, these results underscore that comorbid risk is complex and may differ by molecular subtype. There was a significant association between diabetes and the incidence of Luminal A, Triple-Negative Breast Cancer, and human epidermal growth factor 2−positive breast cancer in Louisiana.
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INTRODUCTION

Breast cancer is the most common form of cancer and the second cause of cancer mortality in women of the U.S.[1] Breast cancer is a group of molecularly and clinically distinct diseases and is classified on the basis of gene expression profiling.[2] A commonly used surrogate for mRNA expression−based classification is based on immunohistochemistry (IHC) for ovarian hormone receptors (HRs) (estrogen receptor [ER] α and progesterone receptor [PR]), erythroblastosis oncogene B2/ human epidermal growth factor 2 (HER2), and proliferative marker Ki-67.[3−5] On the basis of these IHC criteria, breast cancers are often classified into 4 main subtypes: Luminal A (HR+/ HER2−), Luminal B (HR+/HER2+), HER2 enriched (HR−/HER2+), and Triple-Negative Breast Cancer (TNBC) (HR−/ HER2−).[6−8] Luminal B breast cancer has a higher tumor grade by histology and high proliferative index as determined by Ki-67 compared with Luminal A breast cancer, resulting in a worse prognosis.[7,9] TNBC does not express HR, although it can express androgen receptor, nor does it have genomic amplification of the erythroblastosis oncogene B2/*HER2* gene. Clinically aggressive TNBCs that do not respond to neoadjuvant chemotherapy with a pathological complete remission have a high risk of early metastasis and a poor prognosis.[10,11] The HER2-enriched subtype accounts for fewer breast cancer cases and is characterized by high-grade tumors with poor clinical outcomes.[7,12]

Obesity is considered an independent risk factor for several cancers, including breast cancer.[13,14] Globally, the *obese population* (defined with a BMI ≥30 kg/m^2) has grown rapidly in recent decades.[15] The U.S. National Health and Nutrition Examination Survey reported that 40.4% of women were obese.[16] Obesity produces a systemic inflammatory response that releases several cytokines and activates signaling pathways that promote tumor initiation, survival, and immune escape. In addition, estradiol and estrone produced by breast adipocytes can promote the growth of luminal breast cancers.[17] Obesity is a multifactorial condition influenced by several factors, including diet, environment, sociodemographic factors, and physical activity.[18,19] Picon-Ruiz et al. describe in detail the epidemiology and possible mechanistic links between obesity and breast cancer as well as possible risk mitigation interventions, including diet and exercise.[20] The strongest link between obesity and breast cancer incidence has been found in postmenopausal ER-positive breast cancer (reviewed in Picon-Ruiz et al.[20]). By contrast, studies have reported that obesity was associated with lower premenopausal ER-positive breast cancer risk[20−25] or no association at all.[20,26,27] A number of studies indicate that obesity is associated with a higher risk of premenopausal ER-negative breast cancer[22−27] and TNBC,[20,27−33] but the risk is minimally or inversely linked after menopause.[20] There are inconsistent results in describing a correlation between breast cancer development and obesity.[34−38] A recent review described the paradoxical and controversial relationship between obesity and breast cancer, which is influenced by menopausal status.[39] The correlation between obesity and breast cancer risk is also complicated by differences between racial/ethnic groups and sociodemographic factors.[20,24,40−42]

Type 2 diabetes (T2D) is a common comorbidity of obesity, and studies of the relationship between obesity and cancer risks or outcomes do not always distinguish between obesity with and without T2D. Numerous studies support multifaceted associations of diabetes with various cancers, including colorectal, prostate, and breast cancer.[43−46] Diabetes has been reported to be linked with a 17% overall increased risk of breast cancer incidence in women.[43,46] The association was significant among postmenopausal women and with ER+ breast cancer, and it remained significant after adjustment for multiple factors and was independent of age and obesity.[43,46] T2D and obesity were linked with an increased risk for postmenopausal breast cancer.[47−49] Women with diabetes were also reported to be at greater risk of developing TNBC than women without diabetes.[44,50] Multiple factors linked to obesity, metabolic syndrome, and T2D may simultaneously or individually contribute to cancer progression. These include hyperinsulinemia, hyperglycemia, dyslipidemia, insulin-like growth factor, adipokines, and cytokines as well as the gut microbiome.[43,44] Insulin resistance and hyperinsulinism are often associated with obesity but can occur independently of it.[51] Insulin signaling can promote breast cancer growth.[52] Therefore, examining T2D independently of obesity can inform researchers on the possible role of insulin resistance in various subtypes of breast cancer.

In summary, previous studies have produced inconsistent findings on the relationship between obesity and breast cancer development, particularly as it pertains to HR-negative tumors. Most previous studies did not include all breast cancer molecular subtypes and/or had inconclusive results on the association of obesity with breast cancer risk among Black women. Furthermore, limiting the definition of obesity to BMI does not capture the range of dysmetabolism among patients with

obesity. T2D is a frequent metabolic complication of obesity and a diagnosis that can be readily established from electronic health records (EHRs). Louisiana has a high prevalence of obesity, T2D, and breast cancer as well as a diverse population that allows stratification by self-reported race. Therefore, we investigated the association between obesity, diabetes, and the most common breast cancer subtypes by race in Louisiana.

METHODS

Study Population

Data were collected by the Louisiana Tumor Registry (LTR), a participant of the National Cancer Institute's Surveillance, Epidemiology and End Results Program, and the Centers for Disease Control and Prevention's National Program of Cancer Registries. The study included women aged ≥20 years with primary invasive breast cancer (International Classification of Diseases [ICD] for Oncology, third edition site codes C50.0-C50.9) diagnosed from 2010 to 2015. Breast cancers with ICD-O-3 histology codes 9050−9055, 9140, and 9590−9989 diagnosed by autopsy or death certificate were excluded. Eligible case records from LTR were linked to records from the Louisiana Public Health Institute's Research Action for Health Network (REACHnet) to obtain BMI and diagnoses and chronic conditions recorded during patient encounters. REACHnet is an EHR-based clinical data repository that uses the National Patient-Centered Clinical Research Network Common Data Model.[53] All research activities were approved by Louisiana State University Health Sciences Center, New Orleans IRB.

Measures

The molecular subtype was classified on the basis of joint HR status (estrogen/progesterone) and HER2 status. Joint HR status was considered negative if the tumor lacked both estrogen and progesterone reactivity. Borderline hormonal receptor was considered positive. Briefly, the 4 molecular breast cancer subtypes were defined as Luminal A (HR+/HER−), Luminal B (HR+/HER+), Triple Negative (HR−/HER2−), and HER2 (HR−/HER2+).

Patient age was categorized into age groups of 10 years. Self-reported race by patients was categorized as Black or African American, White or European American, or other. BMI was classified as lean (18.5≤BMI<25), overweight (25≤ BMI<30), mild obesity (30≤ BMI<35), and high obesity (BMI≥35). Records with extreme BMI values (>65) were excluded from data summarization to control for potential data entry errors. Diabetes and pregnancy were indicated by ICD, Ninth Revision and ICD-10 diagnoses codes (Appendix Table 2, available online).

Study Design

The study has a retrospective case-control design. Controls were matched to cases on the basis of age and race at a rate of up to 5:1. Matching was performed separately by molecular subtype. Patients who were missing BMI data, underweight (BMI<18.5), or pregnant during the study period were excluded. The stepwise schematic diagram of case and control eligibility for the study is presented in Appendix Figure 1 (available online).

For cases, date of diagnosis, age at diagnosis, race, and molecular subtype were obtained from the LTR database. Obesity status for each patient was determined as the mode or most prevalent BMI category obtained from REACHnet patient records spanning 12 months before diagnosis through 3 months (90 days) after diagnosis. Diabetes and pregnancy status were identified by condition and diagnosis codes from patient encounters in REACHnet that occurred no later than 3 months after the date of diagnosis. Patient information from the EHR was restricted to 3 months after the date of diagnosis to include patients who may have been referred into the health systems shortly after their breast cancer diagnosis while limiting cause-effect bias in the study results.

Controls were selected from a random sample of breast cancer−free patients in REACHnet with at least 1 encounter or visit during the study period. Age and self-reported race were obtained from the medical records, with age observed 12 months after the first encounter. Obesity status for each patient was determined as the mode or most prevalent BMI category across a period of 15 months after the first encounter. Diabetes and pregnancy status were identified by condition and diagnosis codes from patient encounters during the same period (15 months from the first encounter).
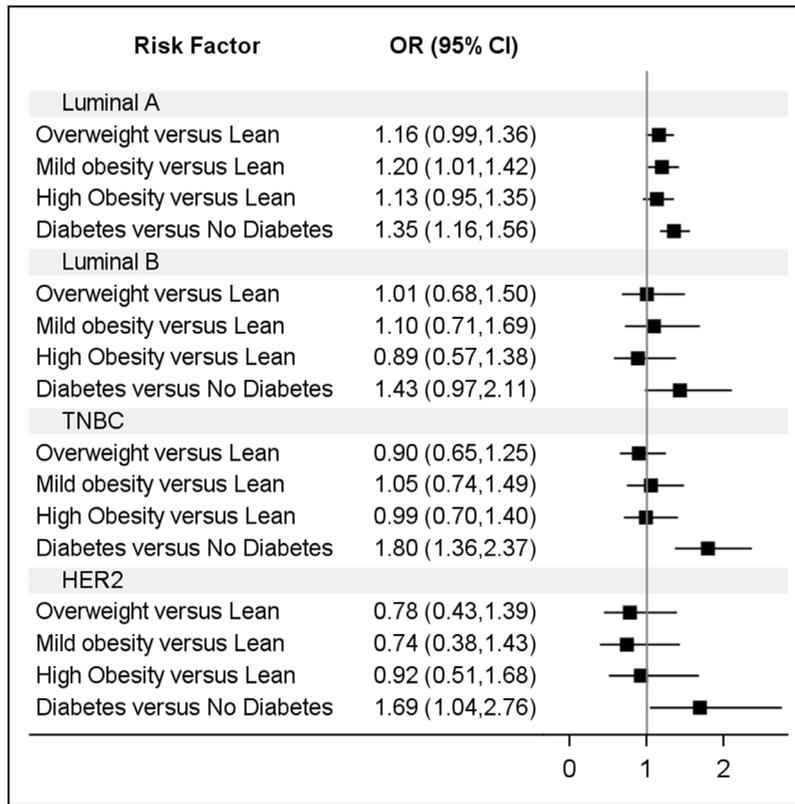
Statistical Analysis

Conditional logistic regression was performed to evaluate the risk factors associated with breast cancer in the case-control sample. This was conducted through effect stratification, with each case and its matched controls constituting 1 stratum.[54] Case-control matching and all data analyses were performed in SAS (SAS Institute Inc, Cary, NC), version 9.4, during 2020−2021. Analyses were executed for each subtype. The primary analysis included 2 logistic regression models with obesity status and diabetes as a single risk factor and a multiple logistic regression with both obesity and diabetes as risk factors (multivariable model). Secondary analyses to confirm the consistency of results from the final model included subanalyses for women aged >50 years and among White/European women and Black/African American women.

RESULTS

Patient characteristics for the cases and controls for each molecular subtype are presented in Table 1. Most breast cancer cases in the study were Luminal A (*n*=1,584). TNBC was the next most common subtype with 364 cases. Luminal B and HER2+ were the least common subtypes with 232 and 115 cases, respectively. Among cases, obesity (mild and high) prevalence ranged from 46.3% (Luminal A) to 51.7% (TNBC). The prevalence of diabetes in cases ranged from 19.8% (Luminal B) to 28.9% (TNBC). Among age- and race-matched controls, the prevalence of obesity ranged from 44.1% to 48.9%, and the prevalence of diabetes ranged from 15.4% to 19%.

The association of obesity and diabetes with breast cancer was assessed with conditional logistic regression models, controlling for age and race matching (Table 2). In the first model, there was an increased risk of obesity among cases compared with that among the controls for Luminal A breast cancer, where the odds of overweight,

Risk Factor	OR (95% CI)
Luminal A	
Overweight versus Lean	1.16 (0.99,1.36)
Mild obesity versus Lean	1.20 (1.01,1.42)
High Obesity versus Lean	1.13 (0.95,1.35)
Diabetes versus No Diabetes	1.35 (1.16,1.56)
Luminal B	
Overweight versus Lean	1.01 (0.68,1.50)
Mild obesity versus Lean	1.10 (0.71,1.69)
High Obesity versus Lean	0.89 (0.57,1.38)
Diabetes versus No Diabetes	1.43 (0.97,2.11)
TNBC	
Overweight versus Lean	0.90 (0.65,1.25)
Mild obesity versus Lean	1.05 (0.74,1.49)
High Obesity versus Lean	0.99 (0.70,1.40)
Diabetes versus No Diabetes	1.80 (1.36,2.37)
HER2	
Overweight versus Lean	0.78 (0.43,1.39)
Mild obesity versus Lean	0.74 (0.38,1.43)
High Obesity versus Lean	0.92 (0.51,1.68)
Diabetes versus No Diabetes	1.69 (1.04,2.76)

Figure 1. AORs and 95% CIs from multivariable conditional logistic regression model.
HER2, human epidermal growth factor 2; TNBC, Triple-Negative Breast Cancer.

Table 1. Patient Characteristics for Breast Cancer Cases and Matched Controls

	Luminal A		Luminal B		TNBC		HER2	
Characteristics	**Cases** (*n*=1,584)	**Controls** (*n*=5,436)	**Cases** (*n*=232)	**Controls** (*n*=1,095)	**Cases** (*n*=364)	**Controls** (*n*=1,686)	**Cases** (*n*=115)	**Controls** (*n*=562)
Age, years								
20–29	0.3 (5)	0.5 (25)	0.4 (1)	0.5 (5)	0.6 (2)	0.6 (10)	0.9 (1)	0.9 (5)
30–39	1.9 (30)	2.7 (149)	7.8 (18)	8.1 (89)	6 (22)	6.5 (110)	6.1 (7)	6.2 (35)
40–49	10.9 (172)	13.8 (748)	19.4 (45)	19.8 (217)	14.6 (53)	14.8 (250)	7.8 (9)	8 (45)
50–59	24.4 (387)	27.1 (1,471)	23.7 (55)	23.8 (261)	26.7 (97)	26.3 (444)	31.3 (36)	31.7 (178)
60–69	31.3 (495)	29.3 (1,591)	26.7 (62)	26.7 (292)	28 (102)	28.1 (473)	31.3 (36)	31.1 (175)
≥70	31.3 (495)	26.7 (1,452)	22 (51)	21.1 (231)	24.2 (88)	23.7 (399)	22.6 (26)	22.1 (124)
Race								
White	69.6 (1,103)	66.6 (3,620)	62.1 (144)	61.4 (672)	50 (182)	51.1 (861)	54.8 (63)	54.6 (307)
Black	28.1 (445)	30.6 (1,662)	35.8 (83)	36.4 (399)	48.9 (178)	47.8 (805)	41.7 (48)	41.8 (235)
Other	2.3 (36)	2.8 (154)	2.2 (5)	2.2 (24)	1.1 (4)	1.2 (20)	3.5 (4)	3.6 (20)
Obesity								
Lean	22.4 (354)	25.8 (1,400)	22.4 (52)	23.1 (253)	21.2 (77)	21.8 (368)	23.5 (27)	21.4 (120)
Overweight	31.4 (497)	30.2 (1,641)	29.7 (69)	29.5 (323)	27.2 (99)	30.5 (514)	27 (31)	29.7 (167)
Mild obesity	23.4 (371)	21.8 (1,183)	24.6 (57)	22.3 (244)	24.5 (89)	22.4 (377)	19.1 (22)	22.2 (125)
High obesity	22.9 (362)	22.3 (1,212)	23.3 (54)	25.1 (275)	27.2 (99)	25.3 (427)	30.4 (35)	26.7 (150)
Type II diabetes								
No	76.8 (1,217)	82.3 (4,476)	80.2 (186)	84.6 (926)	71.2 (259)	81 (1,366)	73 (84)	81.9 (460)
Yes	23.2 (367)	17.7 (960)	19.8 (46)	15.4 (169)	28.9 (105)	19 (320)	27 (31)	18.2 (102)

HER2, human epidermal growth factor 2; TNBC, Triple-Negative Breast Cancer.

Table 2. Results From Case-Control Analyses of Metabolic Risk for Breast Cancer, by Molecular Subtype

Risk factors	Obesity model, OR (95% CI)	Diabetes model, OR (95% CI)	Multivariable model, OR (95% CI)
Luminal A (*n*=1,584)			
Overweight	**1.17 (1.00, 1.38)**		1.16 (0.99, 1.36)
Mild obesity	**1.24 (1.05, 1.47)**		**1.20 (1.01, 1.42)**
High obesity	**1.22 (1.02, 1.45)**		1.13 (0.95, 1.35)
Diabetes		**1.37 (1.19, 1.58)**	**1.35 (1.16, 1.56)**
Luminal B (*n*=232)			
Overweight	1.04 (0.70, 1.54)		1.01 (0.68, 1.50)
Mild obesity	1.14 (0.74, 1.74)		1.10 (0.71, 1.69)
High obesity	0.96 (0.62, 1.48)		0.89 (0.57, 1.38)
Diabetes		1.39 (0.95, 2.04)	1.43 (0.97, 2.11)
TNBC (*n*=364)			
Overweight	0.92 (0.67, 1.28)		0.90 (0.65, 1.25)
Mild obesity	1.13 (0.81, 1.60)		1.05 (0.74, 1.49)
High obesity	1.12 (0.79, 1.57)		0.99 (0.70, 1.40)
Diabetes		**1.82 (1.38, 2.39)**	**1.80 (1.36, 2.37)**
HER2 (*n*=115)			
Overweight	0.82 (0.46, 1.46)		0.78 (0.43, 1.39)
Mild obesity	0.77 (0.40, 1.48)		0.74 (0.38, 1.43)
High obesity	1.03 (0.58, 1.85)		0.92 (0.51, 1.68)
Diabetes		**1.68 (1.05, 2.71)**	**1.69 (1.04, 2.76)**

Note: Boldface indicates statistical significance (*p*<0.05).
Results are provided as ORs and 95% CIs from conditional logistic regression models. Obesity and diabetes models include a single fixed effect for the risk factor of interest. The multivariable model includes both obesity status and diabetes as fixed effects. All models were conditioned on case-control matching (age group 10 years and race).
HER2, human epidermal growth factor 2; TNBC, Triple-Negative Breast Cancer.

mild obesity, and high obesity among cases were 17% −24% greater than those among the controls. There were no significant associations between elevated BMI groups and Luminal B, TNBC, or HER2+ breast cancer subtypes. The second model indicated a significant association between diabetes and breast cancer for Luminal A (OR [95% CI]=1.37 [1.19, 1.58]), TNBC (OR [95% CI]=1.82 [1.38, 2.39]), and HER2+ (OR [95% CI]=1.68 [1.05, 2.71]) subtypes. In multiple logistic regression, including both obesity status and diabetes as independent risk factors, the association between Luminal A breast cancer and overweight (OR [95% CI]=1.20 [1.01, 1.42]) and diabetes (OR [95% CI]=1.35 [1.16, 1.56]) remained significant. Similarly, there were significant associations between diabetes and TNBC (OR [95% CI] =1.8 [1.36, 2.37]) and HER2+ (OR [95% CI]=1.69 [1.04, 2.76]) (Table 2 and Figure 1).

Table 3 contains the conditional OR estimates and 95% CIs from the full case-control sample and subgroup analyses. For Luminal A breast cancer, the association between overweight, mild obesity, and high obesity and breast cancer incidence was most pronounced for women aged ≥50 years, a common proxy for menopausal status, with OR (95% CI) ranging from 1.21

(1.01, 1.43) to 1.33 (1.10, 1.60), and among Black women, with OR (95% CI) ranging from 1.39 (0.96, 2.02) to 1.52 (1.05, 2.20). The association between diabetes and breast cancer was greatest among Black women for Luminal A (OR [95% CI]=1.48 [1.17, 1.87]) and TNBC (OR [95% CI]=1.96 [1.35, 2.85]).

DISCUSSION

In this retrospective case-control study, metabolic risk factors were significantly associated with breast cancer. This study also highlights the heterogeneity of risk factors across breast cancer molecular subtypes. Results indicated that elevated BMI was a risk factor for Luminal A breast cancer, especially in postmenopausal women. In women aged ≥50 years, cases of Luminal A breast cancer had 21%−33% greater odds of presenting with BMI ≥25, which includes the categories of overweight, mild obesity, and high obesity, than controls. These results are in congruence with a body of literature that indicates a positive relationship between body mass and the risk of HR+ breast cancers in postmenopausal women, including several meta-analyses,[31,42,55,56] and although not addressed in this study, literature further

Table 3. Results From Subgroup Case-Control Analyses of Metabolic Risk for Breast Cancer, by Molecular Subtype

Risk factors	All, OR (95% CI)	Age >50 years, OR (95% CI)	White, OR (95% CI)	Black, OR (95% CI)
Luminal A (*n*=1,584)				
Overweight	1.16 (0.99, 1.36)	**1.21 (1.01, 1.43)**	1.10 (0.92, 1.32)	**1.52 (1.05, 2.20)**
Mild obesity	**1.20 (1.01, 1.42)**	**1.33 (1.10, 1.60)**	1.17 (0.96, 1.43)	1.39 (0.96, 2.02)
High obesity	1.13 (0.95, 1.35)	**1.25 (1.03, 1.52)**	1.05 (0.85, 1.30)	**1.47 (1.02, 2.13)**
Diabetes	**1.35 (1.16, 1.56)**	**1.31 (1.13, 1.53)**	**1.33 (1.10, 1.61)**	**1.48 (1.17, 1.87)**
Luminal B (*n*=232)				
Overweight	1.01 (0.68, 1.50)	0.92 (0.57, 1.50)	1.15 (0.73, 1.81)	0.60 (0.26, 1.38)
Mild obesity	1.10 (0.71, 1.69)	1.24 (0.75, 2.05)	1.01 (0.59, 1.72)	0.94 (0.42, 2.11)
High obesity	0.89 (0.57, 1.38)	0.95 (0.56, 1.61)	0.90 (0.52, 1.57)	0.68 (0.30, 1.53)
Diabetes	1.43 (0.97, 2.11)	1.39 (0.91, 2.12)	1.33 (0.76, 2.34)	1.53 (0.88, 2.66)
TNBC (*n*=364)				
Overweight	0.90 (0.65, 1.25)	0.91 (0.63, 1.31)	0.95 (0.63, 1.43)	0.80 (0.45, 1.43)
Mild obesity	1.05 (0.74, 1.49)	1.09 (0.74, 1.61)	1.06 (0.67, 1.69)	1.06 (0.61, 1.86)
High obesity	0.99 (0.70, 1.40)	1.03 (0.69, 1.53)	0.78 (0.47, 1.28)	1.15 (0.67, 1.98)
Diabetes	**1.80 (1.36, 2.37)**	**1.87 (1.39, 2.51)**	**1.68 (1.10, 2.57)**	**1.96 (1.35, 2.85)**
HER2 (*n*=115)				
Overweight	0.78 (0.43, 1.39)	0.77 (0.40, 1.50)	0.60 (0.29, 1.24)	1.03 (0.33, 3.23)
Mild obesity	0.74 (0.38, 1.43)	0.90 (0.44, 1.82)	1.01 (0.46, 2.21)	0.45 (0.12, 1.64)
High obesity	0.92 (0.51, 1.68)	1.17 (0.60, 2.28)	0.62 (0.27, 1.42)	1.17 (0.40, 3.47)
Diabetes	**1.69 (1.04, 2.76)**	**1.66 (1.00, 2.75)**	1.93 (0.95, 3.92)	1.39 (0.68, 2.85)

Note: Boldface indicates statistical significance (*p*<0.05).
Results are provided as ORs and 95% CIs from conditional logistic regression models. All models include both obesity status and diabetes as fixed effects and were conditioned on case-control matching (age group of 10 years and race).
HER2, human epidermal growth factor 2; TNBC, Triple-Negative Breast Cancer.

suggests that this particular relationship is strongest when there is significant weight gain in adulthood.[31,57] In this study, the relationship between elevated BMI and HR− breast cancers was not significant. A consensus on the role of body mass in these breast cancer subtypes has yet to be reached, with contradictory findings in past studies.[42] For instance, a meta-analysis of case-control TNBC studies suggested that body mass is a significant risk factor, but several studies included did not control for race or other covariates.[58] Other meta-analyses of HR− breast cancers found no significant association.[55,56] Conversely, a rigorous study by the African American Breast Cancer Epidemiology and Risk consortium, which aimed to specify the relationship between body type and breast cancer among Black women, found that recently elevated BMI correlated with decreased risk of TNBC.[31] Additional studies have also suggested a protective effect of elevated BMI on HR− breast cancer tumors.[59−62]

Diabetes and prediabetes have been reported as significant risk factors for breast cancer in many populations, with excess risk in the range of 10%−30%.[47−49,63−66] There was a significant association between diabetes and three molecular subtypes of breast cancer in Louisiana—Luminal A, TNBC, and HER2+—in this study. Diabetes exhibited the greatest risk in TNBC, where cases

had 82% greater odds of diabetes than controls. After controlling for obesity status, the OR was nearly unchanged, at 80%. There were similar results for Luminal A and HER2+ subtypes, where the risk associated with diabetes was not attenuated after adjusting for BMI. These results support diabetes as a strong independent risk factor for breast cancer. This contrasts with studies that have reported that the associations between diabetes and breast cancer were attenuated after adjusting for BMI.[47,48,66]

Limitations

Limitations of this study include the retrospective observational study design, which only allows for the determination of association, not causation. The strength of the control population in the study is that it originates from large health systems in the greater New Orleans area, which not only maintain hospitals and emergency departments but also maintain walk-in clinics and urgent-care facilities. However, system-based controls do have the potential for selection bias because this population is more likely to include individuals who receive routine medical care. In the event that the selection bias favors individuals with poorer health status, those who require more frequent care, this would bias results toward the null. The linkage of the EHR records to LTR

to identify breast cancer cases ensured that there was no loss to follow-up among controls. The external validity of the sample is fair because cancer cases were identified through the state cancer registry (LTR) and linked to a large regional EHR network (REACHnet). However, REACHnet does not have complete regional coverage; thus, the sample may not be fully representative.

A distinct objective and strength of this study were to assess metabolic risk factors by molecular subtype. However, low case counts for Luminal B and HER2 molecular subtypes in the study population likely lead to diminished statistical power for these models. The limited sample also precluded the ability to assess risk factors among premenopausal women or postmenopausal women by race. Molecular subtypes were assigned on the basis of IHC commonly used in clinical practice, as opposed to whole-transcriptome gene expression profiling. This prevented an investigation of the molecular subsubtypes of TNBC that are defined strictly through gene expression profiling.

Although the classification of BMI in this study was based on the WHO's classification, it did not differentiate between Class II (35≤ BMI<39.9) and Class III (BMI≥40) obesity owing to low case counts. Instead, these categories were combined into a single category (high obesity), which is consistent with previous literature in the field.[31,67] The *diabetes exposure* was defined by an indication of diabetes in the medical record. This did not include duration or control of disease, which may have the potential to modify risk. Finally, this analysis was limited to data in the National Patient-Centered Clinical Research Network Common Data Model for EHRs and thus did not control for other known risk factors regarding health behaviors (e.g., diet, physical activity), reproductive history, or social determinants of health (e.g., SES, environmental exposures) that were not available in the database.

There are known shortcomings of using BMI as an indicator of obesity in cancer research, with several reviews highlighting the inability of BMI to accurately characterize body composition across races.[42,68,69] The Carolina Breast Cancer Study found that waist−hip ratio was associated with breast cancer incidence in both White and Black women, whereas there was no risk associated with BMI.[70] Unfortunately, other measures of body composition are often not as readily available as BMI, especially in EHR-derived data. Results from this study support the notion that future studies should use multiple or composite measures of metabolic risk that include other comorbid conditions or laboratory profiles, such as Edmonton Obesity staging or metabolic syndrome criteria.[71,72] For example, a meta-analysis found that 3 components of metabolic syndrome—obesity, diabetes,

and hypertension—posed a significant breast cancer risk, and the presence of metabolic syndrome was associated with a twofold increase in breast cancer risk in postmenopausal women.[72]

CONCLUSIONS

There was a significant association between diabetes and the incidence of Luminal A, TNBC, and HER2+ breast cancer in Louisiana. These results suggest that the severity of metabolic sequelae of obesity may be better indicators of breast cancer risk than elevated BMI alone. Future breast cancer research should also consider additional factors that may modify risk in patients with diabetes, such as duration and control of disease, social determinants, and genomic risks.

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SUPPLEMENTAL MATERIAL

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