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Insulin Resistance and Inflammation in Black Women with and without Breast Cancer: Cause for Concern

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Objective: After chemotherapy for breast cancer, Black women gain more weight and have an increased mortality rate compared with White women. Our study objective was to compare biomarkers associated with obesity in Black women with and without a history of breast cancer.

Design: Case-control

Setting: Academic/federal institution

Participants: Black women with a history of breast cancer (cases) and age-matched controls.

Methods: We compared insulin resistance, inflammation, and lipids in overweight and obese Black women with a history of breast cancer (n=19), age similar controls (n=25), and older controls (n=32). Groups did not differ on mean body mass index (BMI), which was 35.4 kg/m^2, 36.0 kg/m^2, and 33.0 kg/m^2, respectively.

Main Outcome Measures: Insulin resistance (HOMA-IR); inflammation (TNF-α, IL-1b, IL-6, IL-8, CRP); lipids (cholesterol, triglycerides).

Results: Cases had 1.6 and 1.38 times higher HOMA-IR values compared with age similar and older controls, respectively (P≤.001 for both). TNF-α and IL-1b were significantly higher in cases compared with both control groups (P<.001 for both). IL-6 was also higher in cases compared with age-similar controls (P=.007), and IL-8 was lower in cases compared with older controls (P<.05). Lipids did not differ between cases and either control group.

Conclusions: Black women with breast cancer were significantly more insulin resistant with increased inflammation compared not only with age similar controls but with women who were, on average, a decade older. These biomarkers of insulin resistance and inflammation may be associated with increased risk of breast cancer recurrence and require ongoing evaluation, especially given the relatively abnormal findings compared with the controls in this underserved group. *Ethn Dis*. 2016;26(4):513-520; doi:10.18865/ed.26.4.513.

Keywords: Health Disparities; Obesity; Breast Cancer; Insulin Resistance; Cancer Survival

Introduction

Most breast cancer (BC) survivors are overweight or obese and approximately 60-80% gain weight during chemotherapy.[1,2] Within two years of BC diagnosis, weight gain between 2 kg and 6 kg[3,4] has been reported. Black women are more likely to be overweight or obese before BC is diagnosed compared with Whites,[5] and they gain more weight following diagnosis and during treatment.[6] In contrast to women of normal weight, those with a high body mass index have twice the risk of BC recurrence and death.[7–9] Consequently, for Black women, who have an increased recurrence risk compared with Whites,[10] obesity is of additional concern.

Obesity is also associated with increased inflammation and may influence the risk of initial BC cancer development as well as its progression.[11,12] Fat tissue functions as a secretory organ for adipokines, protein signals, and other factors, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Inflammation is known to increase cancer cell proliferation and angiogenesis,[13] and IL-6 in particular has been associated with cancer progression and shorter survival in BC.[14]

Obesity is the most common cause of insulin resistance, and elevated blood glucose levels and insulin resistance have been strongly associated with BC recurrence.[15,16]

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In the setting of insulin resistance, various tissues show low cell sensitivity to insulin activity, resulting in a chronic compensatory hyperinsulinemia. By continuously stimulating insulin signalling in sensitive tissues, high levels of circulating insulin cause increased cell division and reduced cell death (anti-apoptosis).[17,18] Age-related declines in insulin sensitivity have been documented,[19] which further compounds insulin resistance progression. Although exact mechanisms remain unknown, hyperinsulinemia and the commensurate increase of insulin-like growth factor may play a role in breast cancer recurrence in insulin-resistant patients.

The purpose of our analysis, therefore, was to compare weight, systemic inflammation, and other associated biomarkers between Black breast cancer survivors and Black women without a history of breast cancer.

Little is known about differences in inflammation and insulin resistance in Black women with and without BC. The purpose of our analysis, therefore, was to compare weight, systemic inflammation, and other associated biomarkers between Black BC survivors and Black women without a history of BC. We hypothesized that measures of inflammation and insulin resistance would be less favorable in women with a history of BC than in those without a history. Specifically, based on what is known in the literature, we expected higher Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values and higher IL-6 and TNF-α in the BC group compared with controls. Our study can provide important information about cardiovascular and metabolic risk factors present in Black BC survivors relative to those without a history of the disease.

Methods

Following University of Maryland Institutional Review Board study approval, recruitment of BC participants was done through oncology practices, community churches and health fairs. Women in the control groups were recruited from the Baltimore/Washington area by advertisements to participate in weight loss and exercise studies.[20] Women in the BC group self-identified as African American or Black, had been previously diagnosed with BC stage I-III, were aged 40-75 years, had no history of diabetes, were post-menopausal, had a body mass index (BMI) ≥25 kg/m^2, had completed adjuvant treatment at least six months prior (with the exception of hormonal therapy), had received medical clearance for study participation from a health care provider, and were English speaking. In the group without BC, women also self-identified as African American or Black, were post-menopausal, had no history of diabetes, and had a BMI ≥25 kg/m^2. Women in the non-BC group were divided into older (aged >57 years) and younger (aged ≤57 years). The younger non-BC group was the primary group for comparison because of similar age. The older non-BC group was also compared with the BC group in order to investigate how a normal aging population compared with the BC group on the measures of interest.

Following informed consent, height (cm) and weight (kg) were measured to calculate BMI. Waist-hip ratio (WHR) was calculated by measuring waist circumference at the narrowest point superior to the hip. This value was divided by the circumference of the hip, measured at its greatest gluteal protuberance. After a 12-hour fast, participants came to the Baltimore Veterans Affairs Medical Center Geriatric Research, Education, and Clinical Center for a blood draw. Blood samples were collected for plasma (heparin) and placed in test tubes. Samples were placed in pre-chilled test tubes containing 1.5 mg EDTA/mL of blood and centrifuged at 2,000 × g for 10 minutes at 4°C.

Biomarker Assays

Plasma glucose concentrations were measured in duplicate using the glucose oxidase method (2300 STAT Plus, YSI, Yellow Springs, OH). Plasma insulin was mea-

Table 1. Population clinical characteristics

Characteristic	Breast Cancer		No Cancer					
	n=19		Similar age, n=25			Older, n=32		
	Mean	SD	Mean	SD	P	Mean	SD	P
Age, years	51.9	8.3	52.8	2.7	.605	63.7	5.0	<.001
Weight, kg	95.1	15.9	99.1	15.1	.404	85.5	11.8	.012
BMI, kg/m^2	35.4	4.2	36.0	5.7	.666	33.0	4.8	.061
Waist-hip ratio	.91	.06	.83	.05	<.001	.81	.08	<.001

BMI, body mass index. Comparisons made to BC group using t-tests. Associated P values are reported.

sured by RIA (Millipore Inc., St. Charles, MO). Homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) was calculated (fasting insulin [µU/mL] x fasting glucose [mmol/L])/22.5 as described by Matthews.[21] Plasma triglyceride and cholesterol were analyzed by enzymatic methods (Hitachi model 917 analyzer), and high-density lipoprotein cholesterol was measured in the supernatant after precipitation with dextran sulfate. Low-density lipoprotein was calculated using the Friedewald equation: LDL-C = total cholesterol – (TG/5 + Hdl-C).[22] All determinations were performed in duplicate (CRP) or triplicate (TNFa, IL-6, IL-8). All assays contained quality control high and low level internal standard pools. Cytokines (TNFa, IL-6, IL-8, CRP) were measured by electrochemiluminescence using a Sector Imager 6000 (Meso Scale Discoveries, Rockville, MD). The inter-assay and intra-assay coefficients of variation (CV) were 10%-15%. Adiponectin was measured by radioimmune assay (Millapore, Inc. St. Charles, MO).

To address skewness of some variables, transformations were done for the following variables: insulin, IL-6, IL-8, and HOMA-IR. Variables reported reflect pre-transformation values. Comparisons of mean values for each measurement were done between the BC group and non-BC comparison groups (older and younger) using independent t-tests. Stata13 was used for statistical analysis (StataCorp, College Station, TX).

Results

The population of women with a history of BC (n=19) had an age range of 40-75, and 42% had been diagnosed within the previous 2 years (range 1-11 years). BC stage at diagnosis included stage I (31.8%), stage II (31.8%), and stage III (27.3%). All women had received either mastectomy or lumpectomy, and most had undergone chemotherapy (81.8%), radiation (77.3%), and hormonal therapy (54.5%). A smaller group (18.2%) had received trastuzamab. The majority (63.6%) had either a college degree or higher. BMI ranged between 27.1-47.2 kg/m^2 for women with a history of BC, and for those without a history of BC the BMI range was 25.3-47.4 kg/m^2. (Table 1)

Comparisons between Women of the Same Age with and without BC

Compared with women without BC and of the same age, fasting insulin levels and HOMA-IR for those with BC were 1.67 and 1.8 times higher, respectively (Table 2; P≤.001 for both). A small but significant relative increase in fasting glucose was also observed in the BC group *(P*=.042). In terms of inflammatory markers, IL-6 and TNFα levels were 1.58 *(P*=.007) and 2.3 *(P*<.001) times higher than the age similar control group, respectively. IL-b was nearly twice that of the age similar controls *(P*=.001). No differences in lipids were noted between these two groups. Waist-hip ratio was 10% higher in the BC group *(P*<.001).

Comparisons between Women with BC and Older Controls

Compared with women without BC in the older control group, fasting glucose levels for those with BC were 1.58 times higher *(P*=.024); insulin was 1.63 times higher and HOMA-IR 1.38 times higher in the BC group *(P*<.001 for both). Inflammatory markers of IL-1b and TNFα were elevated

Table 2. Comparisons on measures of insulin resistance, inflammation and lipids between women with and without breast cancer

Biomarker	Breast cancer		No Cancer					
	n=19		Similar age, n=25			Older, n=32		
	Mean	SD	Mean	SD	P	Mean	SD	P
Glucose, mmol/L	5.78	.84	5.27	.74	.042	5.16	.81	.012
Insulin, μIU/mL[a]	23.4	10.8	15.4	9.9	.001	14.3	7.6	<.001
HOMA-IR[a]	6.0	2.9	3.6	3.1	.001	3.2	1.4	<.001
C reactive protein, mg/dL	8.32	6.90	7.80	6.43	.826	5.09	6.09	.140
IL-1b, pg/mL	2.1	.7	1.1	.9	.001	1.1	.8	<.001
IL-6, pg/mL[a]	6.8	3.6	4.3	3.6	.007	6.7	8.1	.120
IL-8, pg/mL[a]	9.8	5.1	13.1	24.0	.245	10.4	24.2	.018
TNF-α, pg/mL	18.3	5.3	7.8	3.5	<.001	6.8	3.7	<.001
Triglycerides, mg/dL	99.9	58.6	94.7	31.3	.739	114.7	42.9	.324
Total cholesterol, mg/dL	184.4	23.5	189.5	31.0	.580	192.1	31.0	.372
HDL cholesterol, mg/dL	54.5	11.7	56.5	14.9	.669	48.9	9.5	.081
LDL cholesterol, mg/dL	109.5	26.7	114.4	27.8	.594	119.8	27.3	.217
Adiponectin, μg/mL	12.9	8.4, n=17	19.3	9.9, n=11	.082	13.2	9.2, n=9	.938

Comparisons made to BC group using t-tests. Associated P values are reported.
a. Indicates variable transformed for analysis.

in the BC group compared to the older controls (1.9 times and 2.7 times higher, respectively; p<.001 for both). IL-8, conversely, was slightly but significantly higher in the older control group than in the BC group *(P*<.05). No differences in lipids were noted between these two groups. Similar to what was found in the younger control group, waist-hip ratio was also 12% higher in the BC group compared with older control group *(P*<.001).

Discussion

We identified significant insulin resistance in this obese, non-diabetic population of Black BC survivors; this factor may contribute to increased risk of BC recurrence in addition to the well-documented risk of type 2 diabetes. Obese patients often develop insulin resistance, with various tissues showing low cell sensitivity to insulin activity, resulting in a chronic compensatory hyperinsulinemia. By continuously stimulating insulin signalling in sensitive tissues, high levels of circulating insulin cause increased cell division and reduced cell death.[18,23] Although exact mechanisms remain unknown, hyperinsulinemia and the commensurate increase of insulin-like growth factors, may play a role in BC recurrence in insulin-resistant patients. Elevated glucose levels and insulin resistance have been strongly associated with BC recurrence.[15,16]

Our comparisons of the BC group and both control groups (same age and approximately a decade older) revealed that BC patients had markedly higher insulin resistance in both cases, suggesting that BC itself or perhaps aspects of treatment confer additional risk of insulin resistance beyond the normal aging changes. In our population of Black women with a history of BC, HOMA-IR values were much greater than previously reported in the literature. In a sample of 130 Black women with BC and aged 52 (SD±7.4) years, mean HOMA-IR was reported at 4.8, one-third lower than our population of patients of the same age.[24] Similar findings have been reported in a population of 144 Kuwati BC patients, where HOMA-IR values were 28% greater in patients compared with controls (3.6±4 vs 2.6±.5; *P*<.001).[25] Our BC population had 1.6 times higher HOMA-IR values compared with age similar controls. It is possible that length of time from treatment, BC stage, and comorbidities may have played a role in observed insu-

lin resistance in Black BC patients.

Obesity is the most common cause of insulin resistance and may be considered a chronic inflammatory condition. Obesity leads to altered expression of adipokines and cytokines, including TNF-α, IL-6, IL1β.[26] Cancer-associated inflammation also occurs in conjunction with specific cell types, including pro-inflammatory cytokines.[13] As part of this low-grade inflammatory state associated with obesity, overproduction of cytokines may influence the risk of initial BC cancer development as well as its progression.[27] Inflammation is known to increase cancer cell proliferation and angiogenesis.[13] In our study population of Black women, in which each of the three groups did not differ on BMI, TNF-α was significantly higher in the BC group compared with both the age similar and older control groups. The primary role of TNF-α is in regulation of immune cells, and when overproduced, results in a chronic inflammatory state that leads to insulin resistance.[28] Since TNF-α was more than doubled in the BC group compared with the non BC groups, some aspect of the cancer process, in addition to obesity, may drive the elevation. This finding requires further evaluation in future studies.

In the BC group, IL-6 levels were higher compared with the age-similar control group, and IL-8 levels were lower compared with the older control group. IL-6 and IL-8 are additional cytokines associated with both obesity and BC, although their exact role in BC development remains unclear.[12,29] IL-6 expression is positively correlated with obesity and insulin resistance, and IL-6 activation of protein signaling has been shown to stimulate cancer cell proliferation and suppress antitumor activity.[30] Recent studies have demonstrated that upregulated cytokines in the circulation as well as in adipose tissue of obese individuals can stimulate self-renewal and survival of cancer stem cells,[31] which comprise many solid tumors and leukemias and are responsible for tumor initiation and maintenance.[32,33] IL-8 has been associated with development of BC, disease progression, and shorter survival.[14] IL-8 has also been positively associated with estradiol in BC where estradiol increased IL-8. Consequently, the secretion of IL-8 was inhibited post anti-estrogen tamoxifen both in vitro and in vivo in tumors of nude mice, which may offer an explanation for our findings of lower IL-8 in the BC group compared with the older control group.[34]

Our comparisons of the BC group and both control groups (same age and approximately a decade older) revealed that BC patients had markedly higher insulin resistance in both cases, suggesting that BC itself or perhaps aspects of treatment confer additional risk of insulin resistance beyond the normal aging changes.

Upregulation of IL1-β has been documented in the adipose tissue of obese and insulin-resistant mouse models.[35] IL-1-β may also mediate the function of pancreatic beta cells during diabetes development,[36–38] suggesting the role that IL-1-β plays in obesity and insulin resistance. In gliomas, IL1-β is postulated to be responsible for stem cell proliferation, sphere formation, and tumorigenicity,[39] and it is possible that it may have activity in other tumor types.

Adipokines are major contributing factors to both obesity and cancer.[40] Adiponectin is a hormonal growth factor, and epidemiological studies have found an inverse association between adiponectin levels and BC risk.[41–43] Although adiponectin levels were not significantly different between age similar groups in our study (*P*=.08), the reduced number of evaluable participants in the control groups may have affected this analysis. The trend toward lower adiponectin levels in the BC group compared with the age-similar controls suggests a potential association between BC and adiponectin, and we recommend continued surveillance of this important adipokine.

A limitation of this study includes a small sample size of participants with BC relative to each

of the control groups. Although the sample size was sufficient to allow comparisons between groups, more BC participants would have represented this population and may have resulted in a better understanding of some outcomes of interest. For future studies, collecting data about tumor features, such as histologic type and hormone receptor status, may provide additional insights about associations between BC pathology, insulin resistance, and inflammation, which may assist in prioritizing interventions for obesity management.

No measure of total body fat, such as a DEXA scan, was done, which could have provided supporting evidence for our findings. The higher WHR in the BC group relative to both controls, however, provides strong support for our findings of higher HOMA-IR values and inflammation in the setting of greater central obesity, which is consistent with the BC literature.[24]

It is well-established that weight loss can improve insulin sensitivity and reduce inflammation in post-menopausal women without BC.[44–46] Recent work has also revealed decreased circulating levels of IL-8, IL-6 and TNF-α following a weight loss intervention for overweight and obese BC survivors.[11] Although not the focus of this study, our findings indicate that future weight loss intervention work in the BC population should evaluate changes in insulin sensitivity and pro-inflammatory cytokines in order to determine the role of fat mass reduction on markers associated with both obesity and BC risk. For Black women, for whom the recurrence risk looms especially large, these markers are critical.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Griffith, Zhu, Ryan; Acquisition of data: Griffith, Ryan; Data analysis and interpretation: Griffith, Chung, Zhu, Ryan; Manuscript draft: Griffith, Chung, Ryan; Statistical expertise: Chung, Zhu; Acquisition of funding: Griffith, Ryan; Supervision: Griffith, Ryan

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