PREDICTORS AND CONSEQUENCES OF CUMULATIVE STRESS AMONG BLACK BREAST CANCER SURVIVORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

By

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Adana A. M. Llanos, PhD, MPH

And approved by

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ABSTRACT OF THE DISSERTATION

Predictors and Consequences of Cumulative Stress Among Black Breast Cancer Survivors in the Women's Circle of Health Follow-Up Study

by CATHLEEN Y. XING

Dissertation Director:

Adana A. M. Llanos, PhD, MPH

Specific Aims: This doctoral dissertation project was designed to examine two major aims among Black breast cancer (BrCa) survivors enrolled in the Women's Circle of Health Follow-Up Study (WCHFS): 1) to define and quantify allostatic load (AL, as a measure of cumulative physiologic stress) using two computational methods, and identify predictors of AL as measured by both computational methods; and 2) to evaluate the consequences of cumulative stress by examining relationships between AL and BrCa clinicopathological features and quality of life (QoL).

Methods: Black WCHFS participants who were diagnosed with non-metastatic BrCa, completed baseline and follow-up (F/U) interviews, and agreed to the release of medical records were included in this study (n = 409). Data were obtained from in-person interviews and medical records requested from multiple healthcare providers and hospitals. Multivariable-adjusted regression analyses were performed to test the associations among all predictor and outcome variables listed under each specific aim.

Results: AL measure 1 (lipid profile-based measure – assessed by systolic and diastolic blood pressure [SBP, DBP], high-density lipoprotein [HDL], total cholesterol and/or low-density lipoprotein [LDL], triglycerides and glucose levels, waist circumference, and use of medications to treat diabetes, hypertension, or hypercholesterolemia) and AL measure 2 (inflammatory index-based measure – assessed by SBP, DBP, glucose and albumin levels, estimated glomerular filtration rate [eGFR], body mass index [BMI], waist circumference, and use of medications described above) demonstrated moderate-to-fair agreement (kappa=0.504). No significant associations between socioeconomic status (SES), perceived neighborhood characteristics, lifestyle and behavioral factors, and food and nutrient intake with AL measure 1 were observed. Lower SES (namely education and annual household income) was a significant predictor of AL measure 2. With regards to the associations with tumor clinicopathological features, higher AL was found to be a significant predictor of higher tumor grade irrespective of the AL computational methods used. Additionally, larger tumor size was associated with higher AL measure 2. Ultimately, lower QoL assessed by physical well-being (PWB), functional well-being (FWB), and Functional Assessment of Cancer Therapy-General (FACT-G) scales were associated with higher AL measure 2.

Conclusions: Lower individual-level SES is a significant predictor of AL; aggressive tumor clinicopathological features and lower QoL are some of the potential consequences of higher AL among Black women. Research on the causes and consequences of higher levels of cumulative physiologic stress will

be particularly useful in elucidating poorer BrCa outcomes among Black women, and findings from this study may be useful in developing interventional strategies to reduce poorer outcomes among Black BrCa survivors.

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PREDICTORS AND CONSEQUENCES OF CUMULATIVE STRESS AMONG BLACK BREAST CANCER SURVIORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

INTRODUCTION

Cumulative Stress and the "Weathering Hypothesis" in the Context of Chronic Diseases

Cumulative physiologic stress is one of the earliest markers of increased morbidity and mortality risk among older adults in the general population,[1] and poorer health outcomes caused by cumulative stress are particularly prominent among susceptible and disadvantaged individuals (e.g. low SES).[2,3] In 1992, Geronimus proposed the "Weathering Hypothesis," suggesting that cumulative stress caused by low socioeconomic status (SES), is associated with health risks among Black women in early adulthood.[4] It is thought that cumulative stress contributes to various chronic health conditions, and there is empirical evidence that it may ultimately contribute to racial disparities in morbidities, mortalities, and other health outcomes.[5-8] As there is no direct way to measure "weathering" or health deterioration, general health outcome indicators such as mortality and disability have been used to investigate the predictors of weathering and their relationship with health outcomes.[8-10]

One commentary published in 2007 comprehensively discusses how cumulative stress leads to major chronic diseases (e.g., cardiovascular disease [CVD], depression),[2] and several studies suggest that non-cancerous chronic

diseases are important health conditions that could significantly impact cancer progression, quality of life (QoL) and mortality among breast cancer (BrCa) patients.[11-16] Ultimately, Cohen and colleagues concluded that since most published studies mainly focused on the relationships between cumulative stress and different types of cancer together across all racial and ethnic groups, in order to maximize statistical power, more emphasis should be placed on examining how cumulative stress is linked to BrCa risk and progression specifically, as it is the most prevalent cancer among women in Western countries.

Breast Cancer (BrCa) in the United States (U.S.)

BrCa is the most commonly diagnosed cancer and the second leading cause of cancer deaths among women in the United States (U.S.).[17,18] The most recent data estimated that approximately 268,600 new BrCa cases were diagnosed, with 41,760 deaths in the U.S.in 2019.[17] The median age at BrCa diagnosis is about 61 years,[19] and 44% of BrCa cases are diagnosed older than age 65.[20,21] Studies have found that about 1 in 8 American women are expected to develop BrCa in their lifetime, and several BrCa risk factors have been well-documented in the current literature.[22] Evidence shows that age,[17] reproductive characteristics (e.g., early menarche, late or no pregnancy, use of menopausal hormones),[23-25] family history,[26-29] race,[30-33] post-menopausal obesity,[33,34] and behavioral factors (e.g., cigarette smoking and alcohol consumption)[34-39] can affect individual risk of developing BrCa.

The American Cancer Society (ACS) reports that approximately 3.1 million BrCa survivors are currently alive in the U.S.[17] In general, women who are diagnosed with earlier stage breast tumors have a higher 5-year survival rate compared with women who are diagnosed with later stage breast tumors. The 5-year survival rates for Stage 0 (DCIS) and Stage I, Stage II, Stage III and Stage IV (or metastatic stage) are nearly 100%, 93%, 72%, and 22%, respectively.[40]

Among all BrCa cases, White and Black women have higher incidence rates compared to women in other racial/ethnic groups.[17] Although literature prior to 2014 suggested that White women had higher overall BrCa incidence rates than Black women,[41] recent trends have demonstrated the convergence of the BrCa incidence rates for White and Black women.[42,43] Additionally, evidence has shown persistent racial disparities in BrCa clinicopathological characteristics.[44-46]

Among all BrCa subtypes, the triple-negative subtype (TNBC), which is characterized by the lack of expression of the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2), is the most aggressive,[44] and more frequently diagnosed among Black women compared with their White counterparts.[47,48] Moreover, it is also noteworthy that Black women with a history of BrCa show a remarkably higher proportion of BrCa mortality,[17,32,43] younger age at diagnosis,[48,49] lower 5-year survival,[50] increased burden of comorbidities,[51] and worse QoL.[51-56]

It has been widely accepted that low SES is a significant predictor of poorer survival among Black women.[57-60] Evidence has shown that factors related to

low SES (e.g., lack of health insurance, limited access to healthcare) are associated with poorer survival because low SES is likely to cause delayed and inadequate BrCa treatment and follow-up care.[61-65] However, lower BrCa survival rates among Black women still remain significant even after controlling for numerous socioeconomic factors,[31,32,66-70] suggesting that SES is not the only key component contributing to BrCa survival disparities. For instance, one survival study shows no significant relationship between SES and tumor stage in Black women only,[71] and another study demonstrates similar findings related to the association between having a history of screening mammography and stage at BrCa diagnosis among Black women.[72] Moreover, one study suggested that, after controlling for SES, race/ethnicity has no significant impact on survival among Black and White women with TNBC,[73] and further suggests that racial differences in BrCa mortality and 5-year survival rate cannot be solely explained by SES.

Organization of the dissertation

The first objective of this study was to first quantify allostatic load (AL) as a measure of cumulative stress in a sample of Black women who were diagnosed with primary, non-metastatic BrCa, and then to identify predictors of AL in this sample. The second objective was to determine the consequences of AL, particularly focusing on associations with BrCa clinicopathological features, and QoL. We hypothesized that higher AL leads to: (1) more aggressive tumor clinicopathological characteristics; and (2) poorer QoL among Black BrCa survivors (**Figure 1**).

The objectives of this study were accomplished through the following **Specific Aims** and **Hypotheses**, using a sample of Black BrCa survivors enrolled in the WCHFS. The first chapter discusses AL computation using lipid profile-based biomarkers (AL measure 1) and inflammatory-index based biomarkers (AL measure 2), and assesses the concordance of the two AL measures. The next two chapters focus on the potential consequences of AL, namely tumor clinicopathological features and QoL. Hypotheses and specific aims of the three chapters of this dissertation are listed as follows:

Chapter 1:

Specific Aim 1: To define and quantify cumulative stress using two methods to compute AL, and identify predictors of AL among Black BrCa survivors enrolled in WCHFS.

Hypothesis 1.1: Computed AL using AL measure 1 and AL measure 2 will yield similar yet distinctive results.

- **Hypothesis 1.1a**: AL measure 1 and AL measure 2 are statistically concordant.
- **Hypothesis 1.1b**: The associations of high AL scores and all predictors of interest are similar for AL measure 1 and AL measure 2, but more statistically significant findings will be reported for AL measure 2 associations due a larger sample size in the AL measure 2 group.

Hypothesis 1.2: Individual-level SES, neighborhood perceptions, lifestyle and behavioral factors, food and nutrient intake are significant predictors of cumulative stress among Black BrCa survivors.

- **Hypothesis 1.2a**: Women with lower individual-level SES characteristics (low education level, low household income, and Medicaid beneficiaries/uninsured) are at increased risk of experiencing higher AL compared to women with higher SES.
- **Hypothesis 1.2b**: Women who reside in areas that are objectively defined as and/or perceived as more disadvantaged (e.g., perceived as lacking social cohesion, being physically and/or socially disordered, and/or characterized as unsafe) are at increased risk of experiencing higher AL compared to women who reside in areas not perceived as disadvantaged.
- **Hypothesis 1.2c:** Women who practice unhealthy lifestyles and behaviors (e.g., are physically inactive, are current cigarette smokers and are alcohol consumption consumers) are at increased risk of experiencing higher AL compared to women with healthier lifestyle and behaviors.
- **Hypothesis 1.2d:** Women with undesirable food and nutrient intake (e.g., high in saturated fat and/or low in fruit and vegetable) are at increased risk of experiencing higher AL compared to women who consume less saturated fat and/or more fruit and vegetable.

Chapter 2:

Specific Aim 2: To evaluate the consequences of cumulative stress by examining associations between AL and BrCa clinicopathological features among Black BrCa survivors enrolled in WCHFS.

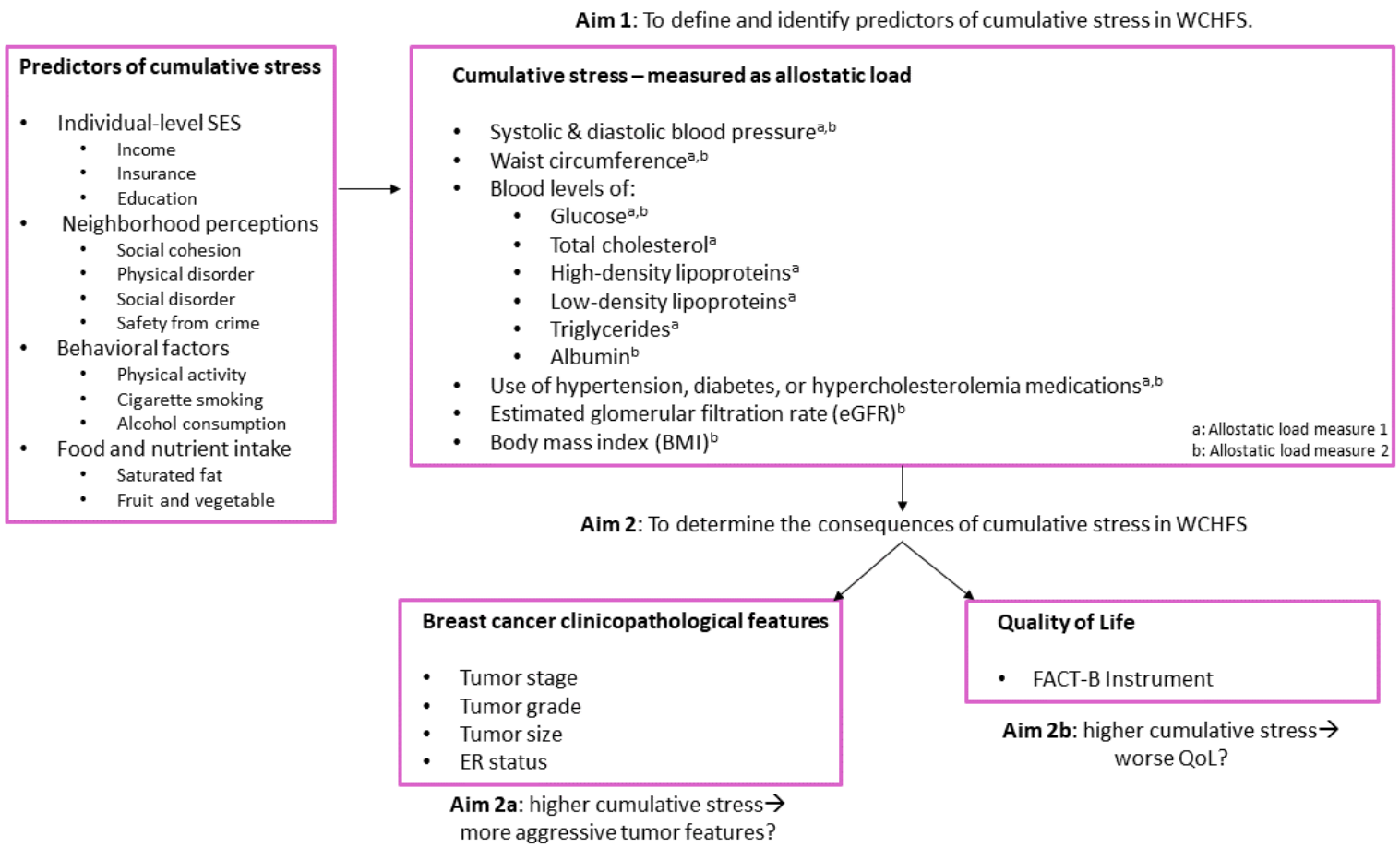
- **Specific Aim 2a**: To explore the associations between cumulative stress and BrCa clinicopathological features that are indicative of aggressive phenotypes among Black BrCa survivors.
  - **Hypothesis 2a:** Women with higher AL have increased odds of being diagnosed with breast tumors that exhibit more aggressive features (invasive tumor behavior, higher grade, larger size, and ER- status), compared to those with lower cumulative stress.

Chapter 3:

Specific Aim 2: To evaluate the consequences of cumulative stress by examining associations between AL and QoL among Black BrCa survivors enrolled in WCHFS.

- **Specific Aim 2b**: To explore associations between cumulative stress and QoL among Black BrCa survivors.
  - **Hypothesis 2b:** Women with higher AL have increased odds of reporting poorer QoL (assessed by FACT-B scales) compared to those with lower cumulative stress.

Figure 1. Conceptual model of the associations of interest and specific aims of the dissertation.



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COMPUTATION AND PREDICTORS OF ALLOSTATIC LOAD AS A MEASURE OF CUMULATIVE STRESS AMONG BLACK BREAST CANCER SURVIVORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

By

CATHLEEN Y. XING

Chapter 1 of 3 of a dissertation entitled

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ABSTRACT OF CHAPTER 1 OF 3

Computation and Predictors of Allostatic Load as a Measure of Cumulative Stress Among Black Breast Cancer Survivors in the Women's Circle of Health Follow-Up Study

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Dissertation Director:

Adana A.M. Llanos, PhD, MPH

Background: Cumulative stress is one of the earliest evidence of increased morbidity and mortality risk among older adults in the general population, and the Weathering Hypothesis suggests that cumulative stress caused by lower SES has disproportionally affected Black women in the United States (U.S.). Cumulative stress can be quantified by using adapted measures of allostatic load (AL) in many ways, however, no previous study has tested the concordance between various AL computation measures, and thoroughly examined how different predictors could potentially contribute to AL among Black women with breast cancer (BrCa).

Methods: Among 409 Black women who were diagnosed with non-metastatic BrCa enrolled in the Women's Circle of Health Follow-Up Study (WCHFS), pre-diagnostic AL scores were calculated using two adapted measures: AL measure 1 (lipid profile-based measure – assessed by systolic and diastolic blood

pressure [SBP, DBP], high-density lipoprotein [HDL], total cholesterol and/or low-density lipoprotein [LDL], triglycerides and glucose levels, waist circumference, and use of medications to treat diabetes, hypertension, or hypercholesterolemia) and AL measure 2 (inflammatory index-based measure – assessed by SBP, DBP, glucose and albumin levels, estimated glomerular filtration rate [eGFR], body mass index [BMI], waist circumference, and use of medications described above). Individual-level socioeconomic status (SES), perceived neighborhood characteristics, lifestyle and behavioral factors, and food and nutrient intake were listed as potential predictors of AL, and multivariable modified Poisson regression models were used to assess the associations of interest among both AL measure groups.

Results: AL measures 1 and 2 demonstrated moderate-to-fair agreement (kappa=0.504). Lower SES, represented by lower educational level and lower annual household income, was found to predict higher AL measure 2. The associations of education and income with AL score were confounded by women's birthplace. There were also suggestive relationships between lower SES higher AL measure 1, albeit with p-value >0.05.

Conclusions: These findings suggest that the lipid profile-based measure of AL and the inflammatory-index based measure of AL are comparable, but also distinct; and lower SES was associated with higher AL among Black BrCa survivors. This study highlights the need for additional research that examines additional predictors of AL.

COMPUTATION AND PREDICTORS OF ALLOSTATIC LOAD AS A MEASURE OF CUMULATIVE STRESS AMONG BLACK BREAST CANCER SURVIVORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

INTRODUCTION

Cumulative Stress – Measured as Allostatic Load (AL)

Objective measures of cumulative stress, including biomarkers (e.g., systolic blood pressure [SBP], diastolic blood pressure [DBP], high-density lipoproteins [HDL], body mass index [BMI]) are recommended to study how physiologic stressors that accumulate through the life course lead to different health outcomes, including BrCa.[1] A process called allostasis (or adaptive response) proposed by Sterling and Eyer describes how the human body's systems release chemical messengers to promote necessary adaptive regulatory processes during exposures to external stressors.[2,3] Allostasis is a necessary component to maintain homeostasis and health status.[4] However, it is important to recognize that allostatic systems can also be problematic if they overreact or fail to function properly, and the term to describe the cost of adaptation is allostatic load.[4,5] In the same year, McEwen defined AL as "the wear and tear on the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptations to environmental challenge."[4] AL serves as a substitute indicator of the cumulative physiological response to stress,[1] which is helpful to better understand the biological mechanisms of how cumulative stress affects morbidity and mortality.[2,3,6,7] According to the allostasis

theory, once the human sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal axis (HPA) are consistently stimulated by various stressors, alterations and disease outcomes in cardiovascular, metabolic and immune systems can be observed.[8,9] Further, the dysregulated allostatic system may disturb the release of certain hormones (e.g., epinephrine and cortisol) and result in elevated blood pressure, making the cardiovascular system most vulnerable.[4,10]

The concept of AL can be represented by biomarkers that are primary mediators (e.g., chemical substances released by human body), secondary outcomes that are observed effects caused by the primary mediators, and tertiary or health outcomes (e.g., morbidity and mortality).[3,5,11-13] For instance, dysregulated stress hormones (primary mediators) cause biologic dysregulation of specific metabolic and cardiovascular biomarkers (secondary outcomes), which ultimately give rise to cardiovascular disease (health outcomes).[3,13,14] AL can be further quantified by using 10 or more measurements gathered from biomarkers (e.g. primary mediators and/or results from those primary mediators),[5,15,16] summed together based on particular risk indices to obtain a single total AL score for a quantitative analysis.[11] Among these measurements, 10 biomarkers are referred by one specific term, called *10 Original Allostatic Load*, which includes a total of 4 primary mediators (plasma urinary-free cortisol, epinephrine, norepinephrine, and dehydroepiandrosterone-sulfate), plus 6 secondary outcomes (systolic blood pressure, diastolic blood pressure, waist to hip ratio, high-density lipoprotein, total cholesterol to high-density lipoprotein

ratio, and glycosylated hemoglobin).[5,9] Furthermore, 6 out of 10 original allostatic biomarkers share similar risk indices that reflect metabolic syndrome such as hyperlipidemia, hypertension, obesity and diabetes mellitus.[17,18]

Based on the concept of AL, researchers have developed measures to quantify cumulative stress, and have sought to explicitly explain how cumulative stress impacts health.[19] Previous studies have supported significant relationships between higher AL scores and lower SES,[5,20-24] aging,[5,15,23] and increased risk of cancer.[1] However, one of the major limitations of using AL to quantify cumulative stress is the heterogeneity in the operationalization and measurement of the various biomarkers that contribute to the quantification of AL,[3] so it is quite challenging to summarize, interpret, and compare findings in current literature.

In general, Black women tend to be more highly susceptible to cumulative stress compared with women in other racial/ethnic groups. In the U.S., Black women aged 35-64 years are shown to have the greatest probability of experiencing high AL scores compared with their White counterparts,[11,25] and remarkable racial gap remains significant across all age strata.[6,26]

There is evidence, although limited, prompting speculation that cumulative stress may also contribute to BrCa etiology and propensity.[27] Studies have shown a significant association between having a history of BrCa and high AL in Black women, suggesting that AL is an important factor that could be potentially linked to BrCa risk and outcomes disparities.[1,26] Ultimately, various health outcomes can be attributed to physiologic, psychological, and socioeconomic

changes caused by numerous stressors among BrCa survivors.[1,28,29] Stress hormones are significantly related to poorer QoL in BrCa survivors, and this finding can be explained by dysregulated endocrine activity.[29] Moreover, high stress is associated with increased risk of mortality and diminished effects of chemotherapy among BrCa survivors.[30-32] Despite the importance of BrCa outcomes disparities, investigations on stressors and the link between cumulative stress and BrCa in Black women are still limited.[33]

Potential Predictors of Cumulative Stress: Individual-Level SES, Neighborhood Perceptions, Lifestyle and Behavioral Factors, and Food and Nutrient Intake

The reasons for BrCa outcomes disparities are likely to be multifactorial.[34,35] Disparities related to BrCa outcomes have been hypothesized to result from combined effects of intrinsic biological factors[36] and non-biological factors.[37] For instance, lower SES has been shown to be related to unfavorable tumor characteristics,[38] suggesting that the consequences of biological factors are impacted by many non-biological factors.[39] One simulation study showed that 38-46% of Black-White BrCa survival disparities are attributed to factors other than age, tumor characteristics, screening, and treatment,[40] and another study further demonstrated that higher socioeconomic deprivation is associated with poorer BrCa survival.[36] Non-biological factors, such as SES, impact BrCa outcome disparities.[36,41-45] However, most studies focus on individual-level SES as the primary contributor,[36,41-50] whereas the impact of neighborhood SES (nSES) and

other area-level characteristics on BrCa outcomes disparities are not well understood.

Several studies have suggested that in addition to individual-level SES, neighborhood characteristics would also help predict health outcomes.[51-55] Evidence has shown that lower nSES is associated with poorer BrCa outcome.[52-54,56,57] Remarkably, one study published by Park et al. provided new insights and highlighted the need for considering perceived neighborhood characteristics to measure area-level SES in BrCa survivors.[58] However, research on perceived neighborhood characteristics among Black BrCa survivors, is very limited. Blacks experience a high degree of residential segregation, which is one of the major causes of racial differences in SES and also plausibly contributes to BrCa outcomes disparities.[59-61] Furthermore, residential segregation has been demonstrated to impact perceived neighborhood disorder through community divestment of a variety of community resources (e.g., access to healthcare, PA resources).[62-65] Social cohesion is also associated with residential segregation and other perceived neighborhood characteristics.[66,67]

Individual-level SES and perceived neighborhood characteristics are potential predictors of cumulative stress. The significant relationship between lower individual-level SES and higher AL in the U.S. population has been demonstrated;[9,20,22,23,68-76] and similar findings have been observed in some European countries as well.[24,72,77] There is also evidence that general neighborhood disadvantage can impact responses to psychological and physiological stress,[78,79] and area-level SES measured by perceived

disadvantaged neighborhood characteristics may be associated with high AL.[58,80-85] Therefore, it is reasonable to posit that dysregulated physical functions may lead to poorer BrCa outcomes.

Physical activity (PA) is a potentially modifiable lifestyle factor shown to be associated with BrCa risk and outcomes.[86-88] Regular PA is safe, feasible and effective for BrCa survivors, which can significantly lower the odds of BrCa and comorbidities (e.g., CVD, type 2 diabetes, and metabolic syndrome)[89] and further improve functional recovery and QoL.[90] Physically active women have significantly reduced BrCa risk compared to physically inactive women.[91-98] Despite the role of PA, adherence to the recommended PA guidelines, is quite low among Black women.[99] Black BrCa survivors are more likely to be obese and physically inactive compared to White women.[99-102] One study has shown that only 54% of Black women reported meeting recommended PA guidelines designed for BrCa survivors, and Black women who have met the PA guidelines showed improved physical functions and reduced pain intensity.[99]

A majority of Black BrCa survivors are physically inactive, however, very few studies have discussed whether or not physically inactive lifestyles impact AL in this group. Very few studies have focused on the associations of PA and AL with mixed results,[103-105] and it was noteworthy that greater leisure-time PA was a significant predictor of lower AL score among White, Black and Latino midlife women.[106] Evidence has shown that cumulative stress is associated with poorer physical and psychological health,[107] and most adverse health outcomes are likely to be at least amendable if early “stress response” are noted with

appropriate actions taken.[108] Previous studies have reported significant associations between chronic stress and sedentary lifestyles,[109,110] but no study has focused on the hypothesized association of lower PA levels with higher cumulative stress among Black BrCa survivors.

Cigarette smoking and[111-113] and alcohol consumption[114-116] are two potentially modifiable behavioral factors shown to be associated with BrCa risk and outcomes. Epidemiological data published from 2000-2011 have shown an association between cigarette smoking and risk of BrCa,[117-121] with a higher risk among pre-menopausal than post-menopausal women.[122] Studies have also shown that an increased risk of BrCa-specific mortality is observed among smokers compared to non-smokers,[123,124] and cigarette smoking may also be related to increased risk of BrCa recurrence,[125] and increased risk of cardiac comorbidities.[126] Similar to cigarette smoking, high levels of alcohol consumption are an established risk factor of BrCa in all women,[127-131] with evidence of a dose-response relationship.[132,133] Biologically, the aldehyde dehydrogenase 1A1 (ALDH1A1) enzyme has important roles in alcohol dependence, alcohol sensitivity, and detoxification after drinking.[134,135] Some in vitro and animal studies have shown that high ALHD1A1 expression is associated with more aggressive breast tumor clinicopathological features, higher likelihood of chemo-resistance and predicted metastasis.[136-138] A recent multi-center, population-based study also demonstrated an association between ALDH1A1 expression and increased BrCa mortality.[139]

Cigarette smoking and alcohol consumption are also potential predictors of cumulative physiological stress. After nicotine ingestion from tobacco, it quickly enters the blood stream and reaches the central nervous system (CNS),[140,141] activates and stimulates the HPA axis, resulting in elevated cortisol level.[142-144] Nicotine can also bind to and activate the nicotine acetylcholine receptors (nAChRs) in the peripheral nervous system (PNS) and some peripheral tissues. Activation of nAChRs in the adrenal medulla may increase catecholamine levels and further result in cardiovascular and metabolic responses, such as increased plasma-free fatty acid release, elevated heart rate, increased blood pressure and increased glucose level.[144,145] Likewise, alcohol consumption is also associated with activation of the HPA axis and increased cortisol levels and cause adverse health outcomes,[146] although alcohol consumption can potentially lower stress levels by promoting more dopamine and β-endorphins secretions through the HPA-axis as well.[147,148] Although substantial studies have investigated the health effects caused by cigarette smoking, alcohol consumption and related biological mechanisms, no previous study has thoroughly examined how cigarette smoking and alcohol consumption affect chronic physiological stress in Black women with BrCa.

The World Health Organizations (WHO) has estimated that about 30-50% of all cancer cases may be prevented by avoiding several risk factors such as unhealthy diet, and diets with fruits and vegetables may show protective effects against many cancers.[149] According to official U.S. dietary guidelines,[150] a healthy eating plan should emphasize fresh fruits and vegetables, whole grains,

low fat or fat-free dairy products, lean meat, poultry, fish, with low saturated fats, trans fats, cholesterol, salt and sugar intake.[151] In the U.S., people with lower SES tend to consume more low-cost foods with higher calories, which have lower nutritional value.[152,153] Excess calories are stored as glycogen or fat in the liver, muscles and adipose cells, and more importantly, visceral fat shows high metabolic activity so more fatty acids, inflammatory agents and hormones are released during metabolism ultimately leading to increases in glucose level, LDL concentration, triglycerides level, and blood pressure.[154]

Unhealthy foods and poor nutrient intakes are associated with increased waist circumference and lower HDL cholesterol concentration,[155,156] which are important components of cumulative physiological stress on the body and contribute to higher AL.[157] Evidence has shown that foods that are high in fat, such as processed meats and French fries, are related to higher AL scores.[158] In contrast, because cumulative stress is associated with oxidative stress, a process that can lead to free radicals and DNA damage,[159,160] consuming larger amounts of fresh fruits and vegetables may potentially reduce cumulative stress.[161,162]

In summary, various physiological stressors can cause dysregulation of primary mediators in the HPA axis, which trigger secondary metabolic and cardiovascular biomarkers,[163] and ultimately lead to chronic diseases.[4,5] Although most of these biomarkers are components of metabolic syndrome, it is noteworthy that the combination of these biomarkers as components of AL are likely to be associated with BrCa outcomes beyond the predictive values of

metabolic disease.[5,17,20,164] In this study, we hypothesized that Individual-level SES, neighborhood perceptions, lifestyle and behavioral factors, and food and nutrient intake are significant predictors of cumulative stress among Black BrCa survivors in Women's Circle of Health Follow-Up Study (WCHFS). To date, no previous study has thoroughly investigated the effects of the aforementioned risk factors on cumulative stress in Black BrCa survivors, so findings from this study will help advance the current state of knowledge.

MATERIALS AND METHODS

The Women's Circle of Health Follow-Up Study (WCHFS): an Overview

The Women's Circle of Health Follow-Up Study (WCHFS)[165] is an ongoing longitudinal study which involves in annual follow-up to evaluate how different factors affect survival and QoL, in relation to obesity, obesity-related comorbidities, and related biomarkers in New Jersey for Black women who were diagnosed since April 2012, and procedures have been described by our previous published studies.[166-168] Briefly, subjects were identified by rapid case ascertained through New Jersey State Cancer Registry (NJSCR). The NJSCR staff contacted newly diagnosed BrCa cases by telephone after contacting their physicians and receiving passive approval to do so. The NJSCR staff explained the WCHFS and obtained verbal consent from these BrCa cases to release their names and contact information to the WCHFS research staff, who were responsible for scheduling the in-person interviews. At the time of all in-person interviews, written informed consent was obtained (before any data collection).

The interviewers were required to explain the study in detail to all study participants, who were encouraged to ask questions during the in-person interviews. Study participants were also informed that they might decline to answer any question(s), stop participating at any time, and call the designated number to report any concerns or withdraw from the study. Access to medical records, pharmacy records and tumor tissue specimen were requested. All study participants received a copy of the consent form and all interviews and biospecimens collections followed standardized protocols.[169]

Samples from in this study were selected based on the following criteria: 1) self-identified as African American or Black; 2) were 20-75 years old; 3) were able to read and understand English; 4) had no history of cancer except non-melanoma skin cancer; 5) were diagnosed with primary, histologically confirmed non-metastatic BrCa in one of ten NJ counties (Bergen, Essex, Hudson, Mercer, Middlesex, Passaic, Union, Monmouth, Burlington, and Camden) usually within 9 months of study enrollment; and 6) were cases who were enrolled in the WCHFS from January 2014 to August 2018.

Baseline and F/U questionnaire data, anthropometric measurements, body composition measures, and biospecimens (saliva and blood) were collected through in-person interviews at 2 different time points: 1) 6-9 months after BrCa diagnosis (baseline interview), 2) 18-24 months after initial diagnosis (F/U-1 interview). During the in-person interviews, baseline and F/U questionnaires were administered by a rigorously trained interviewer, which included structured questions on sociodemographics, reproductive and clinical characteristics,

neighborhood perceptions, comorbidities and medications, and quality of life (QoL). Also, medical records from physicians and hospitals were collected and abstracted, and relevant data (e.g., tumor clinicopathological characteristic from pathology reports) were entered into research databases for further analysis. Additionally, because our study utilized data obtained from baseline and F/U-1 in-person interviews and medical records abstracted at baseline, only study participants who completed the baseline interview and F/U-1 interview and had complete baseline medical records abstracted were included in the analysis.

As of August 15, 2018, 481 Black women with Stage 0, I, II, and III BrCa had completed baseline and F/U-1 interviews (including 110 women who answered the neighborhood questions in F/U-2 interviews to increase the sample size), and agreed to all medical records release at the time of interview. Given that only 47.6% of study participants had lipid tests done within 18 months prior to BrCa diagnosis (or the 1st principle treatment) for the lipid-based AL measure computation (e.g., AL measure 1), a total of 229 cases were available to address all aims and hypotheses in this study using AL measure 1. Alternatively, different biomarkers obtained from routine comprehensive metabolic panel (CMP) could be used to substitute lipid profiles to further increase sample size to n=409 (e.g., AL measure 2). Results obtained from the two aforementioned AL computation groups were reported and discussed separately.

Dependent and Independent Variables

Dependent variable (outcome 1) – AL measure 1 (e.g., lipid-based AL measure): For Aim 1, the main outcome of interest was cumulative stress, measured as AL. Although various biomarkers have been suggested to be components of AL,[5,9,85] a total of 8 biomarkers available in the WCHFS database were selected as contributors to the calculation of the lipid-based AL measure 1 variable in this study. In particular, we used SBP, DBP, waist circumference, glucose level, HDL, LDL, total cholesterol, triglycerides, and use of medications to control hypertension, diabetes, or hypercholesterolemia before BrCa diagnosis as components to define and quantify cumulative stress in Aim 1.[1,9,85]

Waist circumference measurements were available from the baseline in-person assessment. Baseline information on blood pressure, glucose, HDL, LDL, total cholesterol, triglycerides and use of medication were abstracted from medical records, and data on SBP, DBP and lipid profiles were abstracted from the last lab work, which must have been done within 18 months prior to the first principal BrCa treatment (e.g., surgery or neoadjuvant chemotherapy). Additionally, women missing one or more values of the above biomarkers necessary in determining AL measure 1 were excluded from this measurement group, however, they might be eligible for inclusion in the AL measure 2 computation.

Further, previous studies have suggested that AL might be quantified using information gathered from certain biomarkers, summed together based on particular risk indices to obtain a single AL score for quantitative analysis.[1,11,85] In this study, a cut-off value was assigned to each biomarker (e.g., high-risk

threshold), and further recoded as a dichotomous variable (1=if the participant had this condition, 0=if the participant did not have this condition). Based on previous studies, the following cut-off values were used:

- SBP ≥140 mmHg
- DBP ≥90mmHg
- Waist circumference ≥88cm
- Glucose level ≥110mg/dL
- HDL <50mg/dL
- Total cholesterol >240mg/dL or total cholesterol ≤240mg/dL and LDL >130mg/dL
- Triglycerides ≥150mg/dL
- Have ever used medications to control hypertension, diabetes or hypercholesterolemia

Ultimately, points were summed to obtain the AL score, called AL measure 1, with a possible maximum score of 8 (range: 0-8). AL scores were modeled as counted to maximize the power in the analysis.

Dependent variable (outcome 2) – AL measure 2 (e.g., inflammatory-based AL measure): Although 481 WCHFS participants with non-metastatic BrCa were initially eligible, the final sample size for the AL measure 1 group dropped to n=229 because blood levels of HDL, LDL, total cholesterol and triglycerides were not always checked along with routine CMP prior to BrCa diagnosis or the first principle BrCa treatment. Albumin (an inflammatory marker)[85] and GFR (index of

organ dysfunction)[25] were also important biomarkers used to calculate an inflammation-based AL measure with significant results, thus, albumin and GFR could be appropriate substitute biomarkers to replace HDL, LDL, total cholesterol and triglycerides.

In WCHFS, approximately 85% of participants had albumin and GFR results reported with glucose levels by the last CMP work prior to BrCa diagnosis or the first principal treatment, thus, the sample size was increased from 229 to 409 when used biomarkers gathered from CMP for AL measure 2 computation. More importantly, blood levels of HDL, LDL, total cholesterol and triglycerides are likely to be correlated with blood pressure and waist circumference (e.g., indicators of obesity and metabolic syndrome), and in contrast, albumin and GFR are not always associated to obesity-related conditions, so that our study subjects were better balanced. Therefore, it was reasonable to posit that substituting HDL, total cholesterol, LDL and triglycerides (components of metabolic syndrome) with GFR and albumin (biomarkers related to AL but not metabolic syndrome) might lead to similar or more significant findings (e.g., organ failure leads to high mortality).[17,164] Body mass index (BMI) was another biomarker which contributed to the quantification of AL,[1,11,170] and it was available for all Black women who have completed the baseline interview. For this inflammatory-based AL computation, the following cut-off values were used to compute AL measure 2:

- SBP ≥140 mmHg
- DBP ≥90mmHg
- Waist circumference ≥88cm

- Glucose level ≥110mg/dL
- Have ever used medications to control hypertension, diabetes or hypercholesterolemia
- GFR <59 mL/min
- Albumin <4.0g/dL
- BMI ≥30 kg/m^2

As described earlier, the AL measure 2 scores were also summed to obtain a cumulative score along with other aforementioned biomarkers, with a possible maximum score of 8 (range: 0-8). AL measure 2 was also modeled as counted data in the primary analysis for maximized statistical power.

Independent variables (exposures): Detailed information on individual-level SES, perceived neighborhood characteristics, lifestyle and behavioral factors, and food/nutrient intake was available from baseline and F/U-1 (or F/U-2, if neighborhood questions were not provided by the F/U-1 questionnaire) in-person interviews. The following variables were selected to test relevant hypotheses:

- Individual-level SES: questionnaire data related to individual-level SES were selected and categorized based on previously published WCHFS work.[171,172]
    - Annual household income (baseline interview):
        1) <$20,000
        2) $20,000-$69,999
        3) ≥$70,000

- Education level (baseline interview):
    1) Below college
    2) Technical school/some college
    3) College graduate and above
- Primary health insurance: (medical records were used as the primary source, and information gathered from baseline interview was also utilized if information was missing in medical records):
    1) Medicaid
    2) Medicare
    3) Private/employer sponsored
    4) Other (uninsured, missing, or unknown)

- Perceived neighborhood characteristics (F/U interview): questions ascertaining study participants perception of their residential areas were grouped into 3 major subdomains based on previously validated instruments,[66,67,173] with additional questions related to safety and crime, and length of residence (Appendix Table 1). A total of 22 neighborhood questions (with one question related to length of residence) adapted from the validated instruments were selected to determine perceived neighborhood characteristics, and questions were scored so that a high score indicated disorder. In particular, disorder questions were scored as strongly disagree (1 point), somewhat disagree (2 points), neutral (3 points), somewhat agree (4 points), and strongly agree (5 points), and

order questions were scored as strongly agree (1 point), somewhat agree (2 points), neutral (3 points), somewhat disagree (4 points), and strongly disagree (5 points). Question related to women's length of residence was included and utilized in sensitivity analysis. A participant's response was considered as complete and included in the analysis if 80% or more questions were answered listed under the Social Cohesion subdomain, Physical Disorder subdomain, and Social Disorder subdomain. Moreover, the response was also considered as valid and analyzed if the completeness of the Safety and Fear subdomain was above 67% because only 3 questions were related to Safety from crime.

  - Social Cohesion (P1-5; score range: 5-25)
  - Physical Disorder (P6-11; score range: 6-30)
  - Social Disorder (P12-18; score range: 7-35)
  - Safety from crime (P19-21; score range: 3-15)
  - Length of Residence (P22): binary (<2 years, >2 years)

- Lifestyle and behavioral factors: Questions related to weekly PA and smoking history, alcohol consumption were available from the baseline interview:
  - PA: Due to the fact that PA questions included in the WCHFS questionnaire changed greatly since 2012, different PA variables were captured first, and then identified as light activity (e.g., casual walking, dancing, walking at/to/from work), moderate activity (e.g., brisk walk,

swimming, hiking, moderate yard work, carrying a child >50lbs), and vigorous activity (e.g., race walking, jogging, competitive sports, heavy lifting), so that all participants had the same PA variables for data analysis. Next, weekly metabolic equivalents in minutes (METs-min) were calculated using the formula suggested by Andrykowski et al.:[174,175]

Weekly METs-min = [(total minutes of vigorous activity/15) *9 + (total minutes of moderate activity/15)*5 + (total minutes of light activity/15)*3]

Finally, total weekly METs-min were further categorized into 3 different groups for data analysis:

1) <250 METs-min/week
2) 250-499 METs-min/week
3) ≥500 METs-min/week

- Cigarette smoking (baseline interview): a woman was classified as a "never smoker" if she had never smoked at least one cigarette per day for one year. Questions related to age when the participant first started smoking and age at last stop smoking were used to differentiate former smokers and current smokers.
    1) Never smoker
    2) Former smoker
    3) Current smoker

- Alcohol consumption: alcohol consumption data were obtained from selected FFQ variables at the baseline interview, calculated based on total number of alcoholic drinks consumed per week one year prior to BrCa diagnosis.
    1) None
    2) <1 drink/week
    3) ≥1 drinks/week

- Food and nutrient intake (baseline interview): derived data focused daily saturated fat intake, and fruit and vegetable consumption were obtained from the FFQ questionnaire at baseline interview, which captured women's dietary patterns one year prior to BrCa diagnosis. Variables were further dichotomized by using cut-off values suggested by the Dietary Guidelines 2015-2020, 8th edition.
    - Saturated fat intake
        1) <20 grams/day
        2) ≥20 grams/day
    - Fruit and vegetable consumption
        1) <5 servings/day
        2) ≥5 servings/day
- Confounders: a total of 5 potential confounders were included to address all aims and hypotheses in Aim 1 among samples with AL measure 1 and AL measure 2.

- Age at diagnosis (medical records)
- Marital status (baseline interview)
    1) Married or living as married
    2) Separated/divorced/widowed
    3) Single/never married
- Birthplace (baseline interview)
    1) U.S. born
    2) Foreign born
- Menopausal status (baseline interview)
    1) Premenopausal
    2) Postmenopausal
- Family history of breast cancer (baseline interview medical records)
    1) No
    2) Yes

Data Analysis

Data analyses for this chapter included comprehensive descriptive statistics of the study participants (e.g., sociodemographics, reproductive and clinical characteristics, perceived neighborhood characteristics, lifestyle and behavioral factors, food and nutrient intake). Frequencies and proportions for all categorical covariates were reported; means and standard deviations were reported for the continuous covariates. Frequencies, proportions, and means of each marker contributing to AL score were described, and patterns of AL across the study

sample were described among the two AL computation groups. Summary statistics of AL score were reported as well.

For hypothesis 1.1a, kappa statistics was used to test the agreement between AL measure 1 and AL measure 2. In addition to kappa statistics, sensitivity analyses were also performed to examine the associations between AL measure 2 and all predictors among 229 women who had both AL measure 1 and 2, and results were compared with the associations between AL measure 1 and all predictors in the same analytical group, as an additional analytical method to test hypothesis 1.1a. For hypotheses 1.1b and 1.2a-d, multivariable modified Poisson regression analyses were performed to approximate binomial regression models if algorithm did not converge, and incidence rate ratios (IRRs) and 95% confidence intervals (95% CI) were reported to describe the associations between individual-level SES, perceived neighborhood characteristics, lifestyle and behavioral characteristics, food and nutrient intake, and AL, given that AL scores were treated as counted data. Sensitivity analysis of the associations between neighborhood perceptions and AL was performed by using the same multivariable modified Poisson regression model, stratified by length of residence (<2 years vs. 2+ years) to address the concern of a possible reversed temporality as proposed by Hypothesis 1.2b, which was based on the assumption that associations between neighborhood perceptions and cumulative stress did not differ by length of residence. Level of significance will be set to $p=0.05$, and all analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

The distributions of sociodemographics, reproductive, clinical, lifestyle and behavior characteristics are shown in Table 1. The first analytical sample included 229 women with lipid profiles available for AL measure 1 computation, which was a subset of the second analytical sample (n=409). The second analytical sample included all 229 women with AL measure 1, plus an additional 180 women who also had CMP results completed prior to the first principal breast cancer treatment, for AL measure 2 computation. Except for age at diagnosis, the mean values and proportions of sociodemographics, reproductive, clinical, lifestyle, and behavioral characteristics were similar for women with AL measure 1 and AL measure 2, suggesting the similarity between the two analytical groups.

The mean age at breast cancer diagnosis of the sample with AL measure 1 (n=229) was 56.61±9.19 years, and approximately 15% were foreign-born. About one-third of women were married or living as married, had earned a degree from technical/vocational school or some college, and had an annual household income of ≥$70,000. Two-thirds of women had private or employer-sponsored insurance, while 15.28% were enrolled in Medicaid. Nearly 60% were classified as obese (BMI ⩾30kg/m2). Self-reported medical history included age at menarche of ≥13 years for about 26% of the sample. Almost half (43.67%) reported having a family history of breast cancer, a history of oral contraceptive use for more than 75%, and had a history of breastfeeding among 53.5% of parous women. Fewer women reported having a history of hormone replacement therapy use (17.18%) and being nulliparous (12.66%). Most women were

postmenopausal (77.73%) and had at least one or more additional co-occurring health condition present at breast cancer diagnosis (84.28%).

For lifestyle and behavioral characteristics among women with AL measure 1, the mean daily saturated fat intake was 22.79±12.02 grams, including 6.69± 3.61 servings of daily fruit and vegetable consumption. The mean level of PA was 235.56±219.29 METs-min per week. Almost half of the study sample met the daily saturated fat guideline, whereas only 38% women met the guideline for daily fruit and vegetable consumption. Most women were physically inactive, as only 11% met minimum PA guideline of ≥500 METs-min/week. Moreover, about 17% described themselves as current smokers at the time of interview, and 21% reported weekly alcohol consumption one year prior to their breast cancer diagnosis.

Among study participants with AL measure 2 data, the mean age was 55.3±10.40 years, which was mainly driven by the higher proportion in the younger age group and premenopausal group compared to women with AL measure 1 data. More women with AL measure 2 obtained similar levels of education, were nulliparous, and were without comorbidities compared to women with AL measure 1. Like women with AL measure 1, most women with AL measure 2 were U.S. born (85%). Their mean BMI value was 32.05±7.03 kg/m2; with only 13% of women with normal BMI (≤24.99kg/m2). In terms of lifestyle and behavioral characteristics, approximately 60% of women with AL measure 2 classified themselves as never smokers, and distributions of daily saturated fat

intake, fruit and vegetable consumptions, weekly alcohol consumption and physical activity were comparable among women with AL measure 1 and AL measure 2.

The distributions of perceived neighborhood characteristics are reported in Table 2. Overall, mean scores for all individual perceived neighborhood questions, as well as all four subdomains, were all below 3 (e.g., women gave positive and/or neutral neighborhood perceptions), and for most perceived neighborhood questions the mean score was less than 2 (e.g., somewhat agree for an ordered question, or somewhat disagree for a disordered question), indicating that Black WCHFS study participants generally had good perceptions towards their neighborhoods.

Among the AL measure 1 sample, the lowest rated item among all neighborhood questions was related to graffiti, which had a mean score of 1.40±0.89. The highest rated question asked about shared value, which had a mean score of 2.71±1.22. The individual items' mean scores for the 5 social cohesion questions were all between 2 and 3; the mean scores for all 6 physical disorder items ranged from 1.40 to 1.92. The social disorder subdomain had a mean score below 2 for 5 out of 7 questions, and 2 out of 3 safety from crime questions had a mean score ranged from 1 to 2. With respect to length of residence, approximately 90% of women had resided in the same neighborhood for at least 2 years, and only 10.53% women reported having a length of residence less than 2 years.

For women with AL measure 2, all questions listed under the social cohesion subdomain had a mean score between 2 to 3. In addition, questions related to physical disorder had mean scores ranging from 1.43 to 2.00, and 2 out of 3 safety from crime questions had a mean score below 2. It was noteworthy that questions related to trouble with neighbors from the social disorder subdomain had the lowest mean score among all social disorder questions. Ultimately, 90.04% of the sample reported residing in the same neighborhood for more than 2 years, compared to 25 women (9.96%) who reported having a length of residence less than 2 years, respectively.

Table 3 depicts distributions of the various biomarkers contributing to AL measure 1 and AL measure 2. Mean values of total AL score, SBP, DBP, HDL, LDL, total cholesterol, triglycerides, waist circumference, and serum glucose and albumin level were reported. The range for both AL measure 1 and AL measure 2 were 0-7, suggesting that there were no women who fell into the high risk category for all 8 biomarkers in each measure. With respect to individual biomarkers that were originally reported as continuous variables, women with AL measure 1 had higher mean values of SBP, DBP, waist circumference, and glucose level compared to women with AL measure 2. Biomarkers which only contributed to AL measure 1 included HDL, abnormal LDL and/or total cholesterol, and triglycerides. Mean values with standard deviations of HDL, LDL, total cholesterol, and triglycerides were 61.42±17.85 mg/dL, 124.12±106.55 mg/dL, 193.56±38.00 mg/dL and 102.87±52.40 mg/dL, respectively. Serum albumin and BMI were continuous measures that only applied to AL measure 2,

with mean values and standard deviations of 4.41±3.92g/dL for serum albumin level, and 32.05±7.03 kg/m^2 for BMI (also shown in Table 1). Although some lab studies reported eGFR as a continuous variable which contributed to AL measure 2 only, most reports only indicated eGFR >60ml/min for a normal test and was therefore used as a dichotomized measure.

When biomarkers were dichotomized, women with AL measure 1 (65%) had a higher proportion of lower AL compared with AL measure 2 (55.50%). Kappa statistics showed that dichotomized AL measure 1 and 2 had fair-to-moderate agreement (κ=0.504). Further, women with AL measure 1 also had slightly higher proportions of hypertension and larger waist circumference compared to women with AL measure 2 except glucose level, however, those measurements were very similar. With regard to each dichotomized biomarker contributing to AL load score, more than 80% of women with AL measure 1 and 2 had a waist circumference $\geqslant$88cm, and the proportions using medications to control diabetes, hypertension, or hypercholesterolemia were about 77% for women with AL measure 1, and approximately 70% for women with AL measure 2.

Results for unadjusted and multivariate modified Poisson regression analyses examining the associations between individual-level SES related variables, neighborhood perceptions, lifestyle and behavioral characteristics, and cumulative stress are presented in Table 4. Among women with AL measure 1, no significant associations between higher AL scores and lower individual level SES, poorer perceived neighborhood characteristics, and unhealthy lifestyle and behavior factors were reported by unadjusted and adjusted models. Conversely,

several predictors were found to be associated with higher AL score 2. Specifically, among women with AL measure 2 who were born in foreign countries, the risk of observing higher AL was approximately 1.15 times higher among women who did not attend college, and 1.23 times higher among women who had technical school or some college education compared with women who had a college degree. Additionally, the risk of having higher AL 2 score were 17% higher if their annual household income was between $20,000 to $69,999 relative to those whose income was ≥$70,000 if women were non-U.S. born. Ultimately, with regard to lifestyle and behavioral characteristics, the unadjusted analysis showed that among women who reported consuming one or more alcoholic drinks per week had 17% higher AL measure 2, compared to non-drinkers, although this association was not statistically significant in the adjusted model.

Two sets of sensitivity analyses are shown in Table 5 and Table 6. No associations were observed between perceived neighborhood characteristics and AL measure 2. To address the potential issue of reversed temporality, we performed multivariable-adjusted regression analyses (e.g., sensitivity analysis) stratified by length of residence in current neighborhood, between different AL measures and neighborhood perceptions (Table 5). No significant differences in IRRs were observed when analyses were stratified by length of residence. Additionally, given that AL measure 1 (n=229) was a subset of AL measure 2 (n=409), sensitivity analyses were performed by examining the associations of individual-level SES, perceived neighborhood characteristics, lifestyle and behavior factors, food and nutrient intake with AL measure 2 among 229 women

who had both lipid profiles and CMP for the computation of AL measure 1 and AL measure 2 (Table 6). No significant differences in IRRs were reported by Table 6 compared with Table 4, except the association of education with AL measure 2, which was not statistically significant among women with AL measure 1.

DISCUSSION

This is one of the first studies to investigate factors associated with higher cumulative physiological stress among Black women with non-metastatic breast cancer. We found that lower socioeconomic status, namely lower educational level and annual household income, significantly predicted higher AL scores using one of the adapted measures of AL. In particular, contrary to the hypothesis, unhealthy lifestyle and behavior characteristics were not found to be significant predictors of higher AL using measure 1, before or after adjustment for age at diagnosis, birthplace, menopausal and marital status, family history of breast cancer, lower individual-level SES, higher perceived neighborhood disorders. Conversely, using AL measure 2, we found that lower income and education were significantly associated with higher AL. This study however, found no evidence to support the hypothesized association of perceived neighborhood characteristics or lifestyle and behavioral factors with AL.

Cumulative physiological stress can be quantified by calculating AL score, using a variety of up to 16 biomarker measurements.[5,15,16] Hence, there are many ways to estimate AL, and components selected by each study vary greatly depending on data availability. Ideally, using a combination of laboratory results

gathered from a lipid panel (e.g., HDL, LDL, total cholesterol, and triglycerides) along with inflammatory-based biomarkers (e.g., serum albumin or C-reactive protein), anthropometric measurements (e.g., waist circumference), and renal function (e.g., eGFR) to estimate AL score is preferred. These biomarkers represent physiological stress from different systems, thereby providing a more comprehensive measure. In addition, using glycosylated hemoglobin result (e.g., HbA1c test) is preferred over fasting glucose level, as HbA1c can accurately reflect the average glucose level for the past 2-3 months, whereas glucose levels can fluctuate daily.

Theoretically, most of our study participants should have had these lab results available in their medical records, particularly if women get annual physical exams, but unfortunately, only 47% of the study sample had valid lipid profiles available for AL measure 1 computation. Although a total of 481 study participants were initially eligible for inclusion in the current analysis, the sample size was limited to 229 due to a lack of lipid panel results. There are a few possible explanations for this. First, a lipid test is not routinely performed like the case of CMP. CMP is usually checked on the same day when a major breast cancer treatment is performed (e.g., surgery, chemotherapy). For most people, lipid panels are often ordered by a primary care physician (PCP) at the time of annual physical exam; a specialist such an endocrinologist may also order a lipid panel regularly for patients with metabolic syndrome. Thus, a woman may not have lipid panels if she doesn't have a PCP and/or endocrinologist. Secondly, although medical records were obtained from all doctors who had provided care

one year prior through one year after the initial breast cancer diagnosis, lipid profiles could still be missing if a woman did not follow-up with their healthcare providers, or if a lipid panel was not necessary at that time (e.g., a young woman without any co-existing metabolic syndrome related disorders). It should also be noted that some physicians also refused to release their patients' medical records for use in our research study. Therefore, even if a woman had lipid panel results, those data were unavailable to us for inclusion in these analyses.

All studies have included at least one lipid result (HDL, LDL, total cholesterol, and/or triglycerides) for AL score computation in the current literature, and several studies have also considered adding albumin and eGFR to better quantify AL.[25,85] As previously described, abnormal lipid biomarkers (e.g., high LDL, total cholesterol and triglycerides, and low HDL) are strong indicators of metabolic syndrome and obesity, thus, Black WCHFS participants with lipid profiles were likely to be obese with metabolic syndrome related comorbidities. In contrast, albumin and eGFR results abstracted from CMP are also important biomarkers for AL computation, which are not always associated with obesity and metabolic syndrome in general. Thus, in this study, the inclusion of albumin and eGFR results along with BMI allowed us to estimate AL using a second measure and allowed us to increase our sample size, as well as to include more women with fewer co-morbid conditions.

Because no previous studies have ever used hepatic and kidney function tests as alternatives to lipid biomarkers, we proposed to estimate AL using two measures, and compare results to evaluate consistency. Cohen's kappa

coefficient was used to measure agreement between AL measure 1 and 2, indicating a fair-to-moderate agreement (Kappa=0.504). The result was expected because lipid disorders were not directly related to hypoalbuminemia (e.g., low serum albumin) and kidney failure (e.g., low eGFR) within a short period of time. In addition, we also found that the mean AL scores were similar in both AL groups, suggesting that albumin, eGFR, and BMI could possibly substitute for lipid biomarkers, and this partly because Inflammatory markers is associated with obesity, which may be expected to be also associated with dyslipidemia.[176] As Table 4 suggested, although the mean score difference was minimal, a higher proportion of women with AL measure 1 (34.93%) was classified as having high AL (AL score: 4-8) compared to women with AL measure 2 (44.50%). A strong correlation between abnormal lipid profiles and obesity with a high prevalence of obesity in Black women were possible reasons explaining such differences, which was also anticipated.

Based on this study, the relationship of lower SES and higher AL was comparable to previous studies.[6,11,15,22,23,68,75,177] This finding may be partly explained by limited access to healthcare among minorities and disadvantaged individuals, thereby increasing physical and psychological stress (e.g., elevated heart rate and blood pressure). Alternatively, more than 80% Black women in the U.S. are overweight and obese,[178] thereby increasing the risk of higher AL (e.g., abnormal lipid profiles, blood pressure readings, and anthropometrics). Relatedly, limited access to healthcare associated with lower SES likely makes it harder to manage comorbidities. Having good health insurance coverage was

also hypothesized to lower AL scores due to adequate comorbidity management when needed, however, we found no evidence to suggest that insurance type, an indicator of SES, was related to cumulative stress in this study of Black BrCa survivors. Interestingly, it should be noted that Medicare, Medicaid, and other (uninsured or unknown type) all showed inverse associations with higher AL, although these relationships were all found to be not statistically significant. Such effects could be due to differences in out-of-pocket payment. Having private insurance coverage, particularly employer-sponsored insurance, was often indicative of higher SES. However, insurance plans vary greatly, hence a breast cancer patient might still be responsible for an expensive medical bill (e.g., if she had a high-deductible plan). On the other hand, all Medicaid plans were HMO plans without any out-of-pocket payments, therefore, women with Medicaid might not experience as much financial-related stress compared to women with high-deductible private plans.

There is literature, although very limited, suggesting that factors other than individual-level SES may also contribute to cumulative stress. In addition to individual-level SES, the associations between perceived neighborhood characteristics and cumulative stress have been documented.[80-84,179,180] However, our calculated incidence rate ratios (IRRs) hovered around the null with large p-values, which implied that perceived neighborhood characteristics did not affect cumulative stress among Black BrCa survivors using our measures of AL. Since no published studies have examined whether or not perceptions of one's

residential social environment is related to AL among Black breast cancer survivors, further investigations are certainly needed.

Likewise, this study also demonstrated a lack of significant associations between unhealthy lifestyle and behavioral factors and higher cumulative stress, which was also inconsistent with some published studies. For instance, unhealthy behaviors such as cigarette smoking and alcohol consumption may cause high physiological stress by activating the HPA axis with increased cortisol levels, hence leading to adverse metabolic responses.[142-146] Evidence-based studies have shown that regular physical activity could lower the risk of hypertension, abnormal lipid profiles, and metabolic syndrome related disorders,[181] and even greater leisure time physical activity could potentially lower AL and provide better health benefits.[106] Since published studies were mostly based on large health survey data (e.g., NHANES), they might not be specific to Black women with breast cancer. Additional studies with larger samples sizes are needed to clarify these associations.

This study has some limitations that should be considered. First, some information was obtained from questionnaire data, so misclassification could potentially affect the results of this study. For instance, actual prevalence of cigarette smoking among our study sample may have been underestimated,[182] given the fact that the accuracy of self-reported smoking habits is likely problematic for all populations, especially Blacks.[183] Second, prior to the actual data analysis, we performed power calculations, suggesting that this study would be limited by a smaller sample size. Third, about 50% of eligible women for AL

measure 1 computation were excluded from this study due to missing lab results for a variety of aforementioned reasons (e.g., some healthcare providers did not order lipid tests prior to treatment, results were not available for such tests, or healthcare providers refused to release patient medical records which contained these results), so it is unclear whether our study findings are generalizable to all Black BrCa survivors in the United States although the causes of missing lipid profiles may be random. Finally, this study did not account for how medications were used to control hypertension, diabetes, and/or hypercholesterolemia, such as duration, dosage, number of comorbidities being treated, and medication adherence. Therefore, the impact of medications on AL score remains unclear. Nevertheless, this study also has some strengths that should be noted. To our knowledge, this is the first known population-based study to investigate the concordance of two different AL measures, and compare whether or not predictors of high cumulative stress vary depending on how AL is computed. This study is also the first to analyze how factors other than individual-level SES impact cumulative stress among Black women.[36,41-50] Furthermore, our data were available through medical records from various healthcare providers, as well as through annual in-person interviews. As such, accuracy of data received is warranted and further strengthened our study.

In conclusion, this study suggested significant associations between lower SES and higher AL using an inflammatory-index based AL measure, while showing no evidence to suggest significant associations between neighborhood perceptions, unhealthy lifestyles and behaviors, food and nutrient intake, and AL

among Black BrCa survivors, irrespective of the computation method used to estimate AL. Additional longitudinal studies, with larger sample sizes, would be required to further investigate the factors associated with cumulative physiological stress among Black BrCa survivors.

TABLES

Table 1. Sociodemographic, reproductive and clinical characteristics, lifestyle and behavioral factors, and food and nutrient intake among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure 1 (n=229)	**Allostatic Load Measure 2 (n=409)**
Sociodemographics	***n (%)***	***n (%)***
Age at diagnosis (years), mean±SD	56.61±9.19	55.03±10.40
Age at diagnosis		
20-49 years	59 (25.76)	129 (31.54)
50-59 years	74 (32.31)	131 (32.03)
≥60 years	96 (41.92)	149 (36.43)
Birth place		
U.S. born	195 (85.15)	344 (84.11)
Foreign born	34 (14.85)	65 (15.89)
Marital status		
Married or living as married	82 (35.81)	142 (34.72)
Separated/Divorced/Widowed	83 (36.24)	139 (33.99)
Single/Never married	64 (27.95)	128 (31.30)
Education		
Below college	84 (36.68)	142 (34.72)
Technical school/Some college	78 (34.06)	140 (34.23)
College graduate and above	67 (29.26)	127 (31.05)
Annual household income		
<$20,000	59 (26.46)	98 (24.69)
$20,000-69,999	91 (40.81)	173 (43.58)
≥$70,000	73 (32.74)	126 (31.74)
Primary health insurance		
Medicaid	35 (15.28)	55 (13.45)
Medicare	55 (24.02)	82 (20.05)
Private/Employer sponsored	128 (55.90)	246 (60.15)
Other	11 (4.81)	26 (6.35)
Reproductive & clinical characteristics	***n (%)***	***n (%)***
Body mass index (kg/m^2), mean±SD	32.71±7.05	32.05±7.03
Body mass index		
≤24.99 kg/m^2	23 (10.04)	54 (13.20)
25-29.99 kg/m^2	73 (31.88)	127 (31.05)
30-34.99 kg/m^2	51 (22.27)	98 (23.96)
≥35 kg/m^2	82 (35.81)	130 (31.78)
Menopausal status		
Premenopausal	51 (22.27)	120 (29.34)
Postmenopausal	178 (77.73)	289 (70.66)
Age at menarche		
<12 years	62 (27.19)	115 (28.19)
12-13 years	107 (46.93)	189 (46.32)
≥13 years	59 (25.88)	104 (25.49)
Family history of breast cancer		
Yes	100 (43.67)	190 (46.45)
No	129 (56.33)	219 (53.55)
History of oral contraceptive use		
Yes	173 (75.55)	309 (75.55)
No	56 (24.45)	100 (24.45)
History of hormone therapy use		

Yes	39 (17.18)	65 (16.01)
No	188 (82.82)	341 (83.99)
Parity		
Nulliparous	29 (12.66)	75 (18.34)
1-2	114 (49.78)	204 (49.88)
≥3	86 (37.55)	130 (31.78)
History of breastfeeding[a]		
Yes	107 (53.50)	181 (54.19)
No	93 (46.50)	153 (45.81)
Comorbid conditions		
0	36 (15.72)	91 (22.25)
1	68 (29.69)	122 (29.83)
≥2	125 (54.59)	196 (47.92)
Lifestyle and behavioral factors[b]	***n (%)***	***n (%)***
Cigarette smoking		
Never smoker	129 (56.33)	242 (59.17)
Former smoker	61 (26.24)	100 (24.45)
Current smoker	39 (17.03)	67 (16.38)
Alcohol consumption[c]		
None	138 (61.06)	245 (60.49)
<1 drink/week	40 (17.70)	85 (20.99)
≥1 drinks/week	48 (21.24)	75 (18.52)
Physical activity (METs-min/week), mean±SD	235.56±219.29	239.02±233.56
Physical activity[d]		
<250 METs-min/week	158 (69.00)	285 (69.68)
250-499 METs-min/week	46 (20.09)	79 (19.32)
≥500 METs-min/week	25 (10.92)	45 (11.00)
Food and nutrient intake[b]		
Saturated fat (grams/day), mean±SD	22.79±12.02	22.84±12.52
Saturated fat intake[e]		
<20 grams/day	111 (49.78)	197 (49.13)
≥20 grams/day	112 (50.22)	204 (50.87)
Fruit & vegetable (servings/day), mean±SD	6.69±3.61	6.67±3.64
Fruit & vegetable consumption[e]		
<5 servings/day	139 (62.33)	252 (62.84)
≥5 servings/day	84 (37.67)	149 (37.16)

NOTE: Percentages may not sum to 100 due to rounding.

[a] History of breastfeeding were among parous women only.

[b] Lifestyle and behavioral factors, and food and nutrient intake were based on self-report for the time period of one year prior to diagnosis.

[c] The median number of alcoholic drinks reported per week among WCHFS participants was 1 drink and was used as the cut-off point to differentiate between light and moderate/heavy drinkers.

[d] *The Physical Activity Guidelines for Americans, 2008* suggests physical activity of ≥500 METs-min/week for substantial health benefits. An additional cut-off value of 250 METs-min/week was used due to a high percentage of physically inactive women in the study sample.

[e] Cut-off points for daily saturated fat intake and fruits and vegetables consumption were selected according to *Dietary Guideline for Americans, 2015-2020*, 8th edition.

Table 2. Perceived neighborhood characteristics[a] among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure 1[b]	**Allostatic Load Measure 2[c]**
Item Description	***mean±SD***	***mean±SD***
Social Cohesion		
SC1: helpful neighbors	2.01±1.09	2.02±1.12
SC2: close-knit neighbors	2.34±1.14	2.45±1.20
SC3: trustworthy neighbors	2.42±1.17	2.50±1.24
SC4: get along with others	2.17±1.12	2.11±1.07
SC5: share same values	2.71±1.22	2.76±1.19
Total social cohesion score (5-25 points)	11.52±4.16	11.76±4.23
Physical Disorder		
PD1: clean neighborhood	1.92±1.10	1.92±1.12
PD2: houses and yards	1.91±1.12	1.89±1.01
PD3: graffiti	1.40±0.89	1.43±0.91
PD4: noisy neighborhood	1.99±1.40	2.00±1.38
PD5: common vandalism	1.58±1.12	1.61±1.12
PD6: abandoned buildings	1.55±1.10	1.61±1.17
Total physical disorder score (6-30 points)	10.36±5.05	10.46±5.13
Social Disorder		
SD1: many street people	1.73±1.23	1.75±1.27
SD2: high crime rate	1.95±1.34	1.91±1.33
SD3: too much drug use	2.17±1.47	2.14±1.45
SD4: too much alcohol use	2.08±1.41	2.14±1.42
SD5: trouble with neighbors	1.45±0.98	1.38±0.90
SD6: watch out for each other	1.95±1.03	1.98±1.06
SD7: police protection	1.93±1.08	1.96±1.13
Total social disorder score (7-35 points)	13.20±6.18	13.21±6.27
Safety from Crime		
CR1: safe neighborhood	1.86±1.03	1.85±1.06
CR2: safe walk during the day	1.57±0.97	1.52±0.93
CR3: safe walk at night	2.46±1.38	2.41±1.43
Total safety from crime score (5-15 points)	5.86±2.88	5.77±2.91
Length of Residence	***n (%)***	***n (%)***
<2 years	16 (10.53)	25 (9.96)
≥2 years	136 (89.47)	226 (90.04)

NOTE: Percentages may not sum to 100 due to rounding.

[a] See Appendix Table 1 for original questions and item groups. All items were scored so that a higher score indicated a higher perceived neighborhood disorder.

[b] Included Black WCHFS participants (n=152) who responded to F/U neighborhood questions among 229 women with Allostatic load 1 score on or after Dec 11, 2015.

[c] Included Black WCHFS participants (n=251) who responded to F/U neighborhood questions among 409 women with Allostatic load 2 score on or after Dec 11, 2015.

Table 3. Distribution of biomarkers contributing to allostatic load scores among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure 1[a] (n=229)	**Allostatic Load Measure 2[b] (n=409)**
Biomarkers	***mean±SD***	***mean±SD***
Allostatic load score	3.09±1.46	3.15±1.61
Systolic blood pressure (mmHg)	133.47±16.53	130.74±17.14
Diastolic blood pressure (mmHg)	79.70±9.54	78.57±10.18
High density lipoprotein (mg/dL)	61.42±17.85	
Low density lipoprotein (mg/dL)	124.12±106.55	
Total cholesterol (mg/dL)	193.56±38.00	
Triglycerides (mg/dL)	102.87±52.40	
Waist circumference (cm)	103.87±16.62	102.45±15.74
Glucose level (mg/dL)	111.43±54.70	107.39±47.90
Albumin level (g/dL)		4.41±3.92
Biomarkers	***n (%)***	***n (%)***
Allostatic load[c]		
Low (0-3 points)	149 (65.07)	227 (55.50)
High (4-8 points)	80 (34.93)	182 (44.50)
Systolic blood pressure ≥140mmHg		
Yes	79 (34.50)	120 (29.34)
No	150 (65.50)	289 (70.66)
Diastolic blood pressure ≥90mmHg		
Yes	40 (17.47)	64 (15.65)
No	189 (82.53)	345 (84.35)
High density lipoprotein <50mg/dL		
Yes	66 (28.82)	
No	163 (71.18)	
Low density lipoprotein ≥130mg/dL		
Yes	66 (28.82)	
No	163 (71.18)	
Total cholesterol ≥240mg/dL		
Yes	29 (12.66)	
No	200 (87.34)	
Abnormal total cholesterol or LDL level[d]		
Yes	67 (29.96)	
No	162 (70.74)	
Triglycerides ≥150mg/dL		
Yes	29 (12.66)	
No	200 (87.34)	
Glucose level ≥110mg/dL		
Yes	55 (24.02)	106 (25.92)
No	174 (75.98)	303 (74.08)
Waist circumference ≥88cm		
Yes	194 (84.72)	338 (82.64)
No	35 (15.28)	71 (17.36)
History of use of medications to control diabetes, hypertension or hypercholesterolemia		
Yes	177 (77.29)	285 (69.68)
No	52 (22.71)	124 (30.32)
Albumin <4.0g/dL		
Yes		111 (27.14)

No	298 (72.86)
Glomerular filtration rate, <59ml/min	
Yes	38 (9.29)
No	371 (90.71)
Body mass index ≥30kg/m^2	
Yes	228 (55.75)
No	181 (44.25)

NOTE: Percentages may not sum to 100 due to rounding.

[a] Allostatic load measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high-density lipoprotein, triglycerides, total cholesterol and/or low-density lipoprotein, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[b] Allostatic load measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[c] The median allostatic load score among Black WCHFS participants was 3. Thus, 3 was used as the cut-off point to dichotomize the allostatic load variable.

[d] Abnormal total cholesterol or LDL level was defined as: 1) total cholesterol >240mg/dL or 2) total cholesterol ≤240mg/dL and LDL >130mg/dL.

Table 4. Univariable and multivariable[a] modified Poisson regression analyses of the associations between individual-level SES, perceived neighborhood characteristics, lifestyle and behavioral factors, food and nutrient intake with allostatic load among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure 1[b] *IRR (95% CI)*		**Allostatic Load Measure 2[c]** *IRR (95% CI)*	
	Univariable	**Multivariable**	**Univariable**	**Multivariable**
Individual-level SES				
Education				
Below college	1.03 (0.88,1.20)	0.99 (0.85,1.16)	**1.24 (1.09,1.40)**	**1.15 (1.02,1.30)**
Technical school/Some college	1.14 (0.97,1.32)	1.11 (0.95,1.30)	**1.30 (1.15,1.47)**	**1.23 (1.09,1.39)**
College graduate and above	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
	P = 0.2160	P = 0.2644	**P < 0.0001**	**P = 0.0030**
Annual household income				
<$20,000	1.05 (0.89,1.24)	1.03 (0.85,1.24)	**1.20 (1.05,1.37)**	1.14 (0.98,1.32)
$20,000-69,999	1.13 (0.97,1.30)	1.08 (0.92,1.27)	**1.22 (1.09,1.37)**	**1.17 (1.03,1.33)**
≥$70,000	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
	P = 0.2488	P = 0.5779	**P = 0.0022**	**P = 0.0443**
Primary health insurance at diagnosis				
Medicaid	1.00 (0.72,1.38)	0.99 (0.72,1.37)	1.01 (0.80,1.28)	0.92 (0.72,1.15)
Medicare	1.08 (0.79,1.46)	0.95 (0.68,1.31)	1.19 (0.96,1.48)	0.91 (0.72,1.14)
Private/Employer sponsored	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Other	0.97 (0.72,1.29)	0.95 (0.71,1.29)	0.91 (0.74,1.12)	0.85 (0.69,1.04)
	P = 0.5568	P = 0.9966	P = 0.3303	P = 0.3352
Perceived neighborhood characteristics				
Social cohesion	0.99 (0.97,1.01)	0.99 (0.97,1.01)	1.00 (0.98,1.01)	0.99 (0.98,1.01)
	P = 0.4195	P = 0.4354	P = 0.5857	P = 0.4206
Physical disorder	1.00 (0.98,1.01)	1.00 (0.99,1.02)	1.00 (0.98,1.01)	1.00 (0.99,1.01)
	P = 0.8092	P = 0.8819	P = 0.4745	P = 0.8467
Social disorder	1.00 (0.99,1.01)	1.00 (0.99,1.01)	1.00 (0.99,1.01)	1.00 (0.99,1.01)
	P = 0.9543	P = 0.8288	P = 0.6072	P = 0.8767
Safety from crime	0.99 (0.97,1.01)	1.00 (0.97,1.02)	0.99 (0.97,1.01)	1.00 (0.98,1.02)
	P = 0.4380	P = 0.7254	P = 0.5403	P = 0.8345

Table 4 (Cont'd). Univariable and multivariable[a] modified Poisson regression analyses of the associations between individual-level SES, perceived neighborhood characteristics, lifestyle and behavioral factors, food and nutrient intake with allostatic load among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

Lifestyle & behavioral factors[d]				
Cigarette smoking				
Never smoker	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Former smoker	1.07 (0.89, 1.29)	1.15 (0.95,1.38)	0.95 (0.81,1.11)	1.04 (0.89,1.22)
Current smoker	0.93 (0.80, 1.07)	1.00 (0.86,1.16)	0.93 (0.83,1.04)	1.09 (0.96,1.22)
	P = 0.1860	P = 0.2513	P = 0.4668	P = 0.3815
Alcohol consumption[e]				
None	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
<1 drink/week	0.97 (0.78,1.19)	0.97 (0.79,1.20)	1.04 (0.88,1.22)	1.02 (0.87,1.20)
≥1 drinks/week	1.16 (0.98,1.37)	1.13 (0.96,1.34)	**1.17 (1.02,1.33)**	1.10 (0.97,1.25)
	P = 0.1101	P = 0.1089	**P = 0.0302**	P = 0.2222
Physical activity[f]				
≤250 METs-min/week	1.08 (0.88,1.32)	1.05 (0.86,1.29)	1.04 (0.88,1.22)	0.98 (0.84,1,15)
251-499 METs-min/week	0.94 (0.74,1.19)	0.91 (0.72,1.16)	0.90 (0.74,1.09)	0.86 (0.72,1.04)
≥500 METs-min/week	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
	P = 0.7493	P = 0.6591	P = 0.3063	P = 0.2636
Food and nutrient intake[d]				
Saturated fat intake[g]				
<20 grams/day	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
≥20 grams/day	0.95 (0.84,1.08)	0.93 (0.82,1.06)	0.99 (0.90,1.10)	0.96 (0.87,1.06)
	P = 0.4409	P = 0.2645	P = 0.8533	P = 0.4696
Fruit and vegetable consumption[g]				
<5 servings/day	1.02 (0.90,1.16)	1.03 (0.90,1.17)	1.06 (0.95,1.17)	1.06 (0.96,1.17)
≥5 servings/day	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
	P = 0.2061	P = 0.2326	P = 0.0919	P = 0.1041

[a] The following confounders were included in the multivariable analysis: 1) age at diagnosis, 2) birthplace, 3) marital status, 4) menopausal status and 5) family history of breast cancer.

[b] Allostatic Load Measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high-density lipoprotein, triglycerides, total cholesterol and/or low-density lipoproteins, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[c] Allostatic Load Measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[d] Lifestyle and behavioral factors, and food and nutrient intake were based on self-report for the time period of one year prior to diagnosis.
[e] The median number of alcoholic drinks reported per week among WCHFS participants was 1 drink and was used as the cut-off point to differentiate between light and moderate/heavy drinkers.
[f] The Physical Activity Guidelines for Americans, 2008 suggests physical activity of ≥500 METs-min/week for substantial health benefits. An additional cut-off value of 250 METs-min/week was used due to a high percentage of physically inactive women in the study sample.
[g] Cut-off points for daily saturated fat intake and fruits and vegetables consumption were selected according to Dietary Guideline for Americans, 2015-2020, 8th edition.

Table 5. Sensitivity analysis. Multivariable[a] modified Poisson regression analyses of the associations between perceived neighborhood characteristics with allostatic load among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods and stratified by length of residence.

	Allostatic Load Measure 1[b,c]		**Allostatic Load Measure 2**[d,e]	
	Length of Residence		**Length of Residence**	
Perceived neighborhood characteristics	**≥2years** ***IRR (95%CI)***	**<2years** ***IRR (95%CI)***	**⩾2years** ***IRR (95%CI)***	**<2years** ***IRR (95%CI)***
Social cohesion	0.99 (0.98,1.01) p=0.5033	0.89 (0.78,1.02) p=0.0947	0.99 (0.98,1.01) p=0.2653	1.00 (0.94,1.08) p=0.8645
Physical disorder	1.00 (0.99,1.02) p=0.7004	0.96 (0.90,1.03) p=0.2469	1.00 (0.99,1.01) p=0.7701	0.99 (0.94,1.04) p=0.6568
Social disorder	1.00 (0.99,1.02) p=0.6955	0.98 (0.92,1.03) p=0.4021	1.00 (0.99,1.01) p=0.6917	1.00 (0.96,1.04) p=0.8693
Safety from crime	1.00 (0.97,1.02) p=0.7997	0.95 (0.85,1.07) p=0.4009	1.00 (0.98,1.02) p=0.8404	1.03 (0.94,1.12) p=0.5314

[a] The following confounders were included in the multivariable analysis: 1) age at diagnosis, 2) birthplace, 3) marital status, 4) menopausal status and 5) family history of breast cancer.

[b] Allostatic Load Measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high-density lipoprotein, triglycerides, total cholesterol and/or low-density lipoprotein, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[c] Included Black WCHFS participants (n=152) who responded to F/U neighborhood questions among 229 women with Allostatic load 1 score on or after Dec 11, 2015.

[d] Allostatic load measure 2 is computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[e] Included Black WCHFS participants (n=251) who responded to F/U neighborhood questions among 409 women with Allostatic load 2 score on or after Dec 11, 2015.

Table 6. Sensitivity analysis. Univariable and multivariable[a] modified Poisson regression analyses of the associations between individual-level SES, perceived neighborhood characteristics, lifestyle and behavioral factors, food and nutrient intake with allostatic load measure 2 among Black breast cancer survivors with both allostatic load measure 1[b] and allostatic load measure 2[c] in the Women's Circle of Health Follow-Up Study (WCHFS), n=229

	Allostatic Load Measure 2[c] *IRR (95% CI)*	
	Univariable	**Multivariable**
Individual-level SES		
Education		
Below college	1.05 (0.90,1.23)	1.42(0.87,1.19)
Technical school/Some college	**1.26 (1.09,1.47)**	**1.23 (1.06,1.43)**
College graduate and above	1.00 (Referent)	1.00 (Referent)
	P = 0.0041	**P = 0.0060**
Annual household income		
<$20,000	1.14 (0.95,1.31)	1.09 (0.90,1.31)
$20,000-69,999	**1.19 (1.03,1.37)**	1.13 (0.96,1.32)
≥$70,000	1.00 (Referent)	1.00 (Referent)
	P = 0.0603	P = 0.3246
Primary health insurance at diagnosis		
Medicaid	1.02 (0.68,1.51)	1.04 (0.70,1.54)
Medicare	1.12 (0.79,1.58)	0.97 (0.68,1.40)
Private/Employer sponsored	1.00 (Referent)	1.00 (Referent)
Other	0.94 (0.68,1.32)	0.92 (0.66,1.29)
	P = 0.1374	P = 0.7299
Perceived neighborhood characteristics		
Social cohesion	0.99 (0.98,1.01)	1.00 (0.99,1.01)
	P =0. 6923	P = 0.5826
Physical disorder	1.00 (0.98,1.01)	1.00 (0.99,1.02)
	P = 0.6921	P = 0.8584
Social disorder	1.00 (0.99,1.01)	1.00 (0.99,1.01)
	P = 0.7216	P = 0.9992
Safety from crime	0.99 (0.97,1.01)	1.00 (0.97,1.02)
	P = 0.5077	P = 0.8131
Lifestyle & behavioral factors[d]		
Cigarette smoking		
Never smoker	1.00 (Referent)	1.00 (Referent)
Former smoker	1.00 (0.83, 1.21)	1.06 (0.87,1.28)
Current smoker	1.05 (0.91, 1.21)	1.16 (1.00,1.34)
	P = 0.7691	P = 0.1223
Alcohol consumption[e]		
None	1.00 (Referent)	1.00 (Referent)
<1 drink/week	0.95 (0.78,1.17)	0.97 (0.79,1.18)
≥1 drinks/week	1.10 (0.93,1.30)	1.08 (0.91,1.27)
	P = 0.1398	P = 0.3405
Physical activity[f]		
≤250 METs-min/week	1.09 (0.89,1.33)	1.04 (0.85,1.28)
251-499 METs-min/week	0.99 (0.78,1.25)	0.95 (0.75,1.21)
≥500 METs-min/week	1.00 (Referent)	1.00 (Referent)
	P = 0.4084	P = 0.5232
Food and nutrient intake[d]		
Saturated fat intake[g]		

<20 grams/day	1.00 (Referent)	1.00 (Referent)
≥20 grams/day	0.97 (0.88,1.10)	0.96 (0.84,1.09)
	P = 0.6495	P = 0.4916
Fruit and vegetable consumption[g]		
<5 servings/day	1.06 (0.93,1.21)	1.08 (0.95,1.23)
≥5 servings/day	1.00 (Referent)	1.00 (Referent)
	P = 0.3545	P = 0.2485

[a] The following confounders were included in the multivariable analysis: 1) age at diagnosis, 2) birthplace, 3) marital status, 4) menopausal status and 5) family history of breast cancer.

[b] Allostatic Load Measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high-density lipoprotein, triglycerides, total cholesterol and/or low-density lipoproteins, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[c] Allostatic Load Measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[d] Lifestyle and behavioral factors, and food and nutrient intake were based on self-report for the time period of one year prior to diagnosis.

[e] The median number of alcoholic drinks reported per week among WCHFS participants was 1 drink and was used as the cut-off point to differentiate between light and moderate/heavy drinkers.

[f] The Physical Activity Guidelines for Americans, 2008 suggests physical activity of ≥500 METs-min/week for substantial health benefits. An additional cut-off value of 250 METs-min/week was used due to a high percentage of physically inactive women in the study sample.

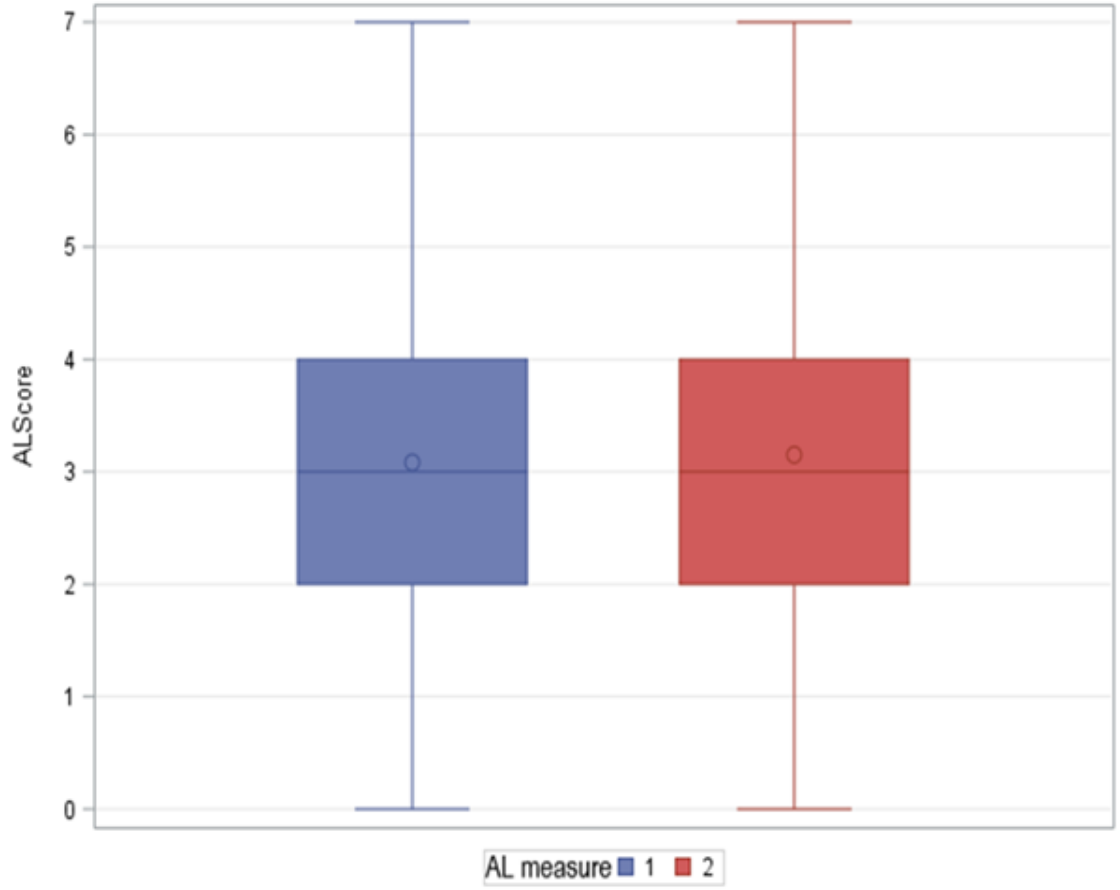
[g] Cut-off points for daily saturated fat intake and fruits and vegetables consumption were selected according to Dietary Guideline for Americans, 2015-2020, 8th edition.

Appendix Table 1. Validated items measuring perceived neighborhood characteristics among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS).

Social cohesion	
CH1[a]	People around here are willing to help their neighbors.
CH2[a]	This is a close-knit neighborhood.
CH3[a]	People in this neighborhood can be trusted.
CH4[b]	People in this neighborhood generally do not get along with each other.
CH5[b]	People in this neighborhood do not share the same values.
Physical disorder	
PD1[a]	This neighborhood is clean.
PD2[a]	People in my neighborhood take good care of their houses/apartments and yards.
PD3[b]	There is a lot of graffiti in this neighborhood.
PD4[b]	This neighborhood is noisy.
PD5[b]	Vandalism is common in this neighborhood.
PD6[b]	There are lots of abandoned/boarded buildings in my neighborhood.
Social disorder	
SD1[b]	There are too many people hanging around on the streets near my home.
SD2[b]	There is a high crime rate in this neighborhood.
SD3[b]	There is too much drug use in my neighborhood.
SD4[b]	There is too much alcohol use in my neighborhood.
SD5[b]	I'm always having trouble with my neighbors.
SD6[a]	In my neighborhood, people watch out for each other.
SD7[a]	The police protection in my neighborhood is adequate.
Safety from Crime	
CR1[a]	This neighborhood is safe.
CR2[a]	I feel safe waking in this neighborhood during the day.
CR3[a]	I feel safe waking in this neighborhood at night.
Length of Residence	
Length	Years I have lived in this current neighborhood

[a] Indicates order items and are scored as followed: 1, strongly agree; 2, somewhat agree; 3, neutral; 4, somewhat disagree; and 5, strongly disagree.
[b] Indicates disorder items and are scored as followed: 1, strongly disagree; 2, somewhat disagree; 3, neutral; 4, somewhat agree; and 5, strongly agree.

Figure 1. Concordance between allostatic load measure 1 and allostatic load measure 2 among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS). Cohen's kappa coefficient, measuring agreement between AL measure 1 and AL measure 2 indicated a fair-to-moderate agreement (Kappa=0.504).



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ASSOCIATIONS OF TUMOR CLINICOPATHOLOGICAL FEATURES AND ALLOSTATIC LOAD AMONG BLACK BREAST CANCER SURVIVORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

By

CATHLEEN Y. XING

Chapter 2 of 3 of a dissertation entitled

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ABSTRACT OF CHAPTER 2 OF 3

Associations of Tumor Clinicopathological Features and Allostatic Load Among Black Breast Cancer Survivors in the Women's Circle of Health Follow-Up Study

by CATHLEEN Y. XING

Dissertation Director:

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Background: In the U.S., Black women tend to have higher cumulative physiological stress compared with women of other races/ethnicities, which may contribute to aggressive breast cancer (BrCa) clinicopathology. However, few empirical studies have tested this hypothesis among Black women. The aim of this study is to examine the association of allostatic load (AL; as a measure of cumulative physiological stress) and BrCa clinicopathology among Black women with BrCa.

Methods: In a sample of 409 Black women with non-metastatic BrCa enrolled in the Women's Circle of Health Study, pre-diagnostic AL were computed using two adapted measures: AL measure 1 (lipid profile-based) and AL measure 2 (inflammatory index-based measure), described in Chapter 1 of this study. Tumor behavior, tumor grade, tumor size, and estrogen receptor (ER) status were selected as important components of tumor characteristics, and multivariable-

adjusted logistic regression models were applied to assess the associations of interest.

Results: Higher AL was found to be a significant predictor of higher tumor grade (poorly differentiated vs. well/moderately differentiated) using AL measure 1 (OR=2.16; 95% CI: 1.18 to 3.94) and AL measure 2 (OR=1.60; 95% CI: 1.02 to 2.51). Higher AL measure 2 was also a significant predictor of larger tumor size (≥2cm vs. <2cm; OR=1.58; 95% CI: 1.01 to 2.46), and these associations were confounded by age. There were also suggestive relationships between higher AL and invasive tumor behavior and ER- status, albeit with p-value >0.05.

Conclusions: This is the first study suggesting that unfavorable BrCa clinicopathological characteristics, namely higher tumor grade and larger tumor size, are potential consequences of higher AL among Black BrCa survivors. These preliminary findings contribute to important gaps in knowledge related to the mechanisms involved in the development of aggressive BrCa phenotypes.

ASSOCIATIONS OF TUMOR CLINICOPATHOLOGICAL FEATURES AND ALLOSTATIC LOAD AMONG BLACK BREAST CANCER SURVIVORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

INTRODUCTION

Breast tumor clinicopathological characteristics include tumor stage, tumor behavior, tumor grade, tumor size, receptor status, and molecular subtype. The Tumor, Node, Metastasis (TNM) staging system proposed by the American Joint Committee on Cancer (AJCC) is one internationally accepted staging system being used to determine tumor anatomic staging and prognosis.[1,2] Each tumor is assigned to a specific tumor grade (e.g., low, intermediate, and high) based on cell morphology and differentiation. Estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status with Ki-67 information from the immunohistochemistry (IHC) analysis can divide BrCa into 4 major molecular subtypes, including luminal A, luminal B, non-luminal HER2 overexpressing, and basal-like.[3,4] The basal-like subtype is one major subset of the TNBC subtype[5] and is associated with the worst prognosis among all BrCa subtypes.[6,7] Interestingly, the TNBC subtype is more prevalent among women with BRCA1 mutation and young Black women,[8-12] and a higher incidence of TNBC in Black women is thought to be an independent predictor of BrCa survival outcome.[13] However, some conflicting Black/White studies have suggested that the BrCa survival disparities cannot be fully explained by a higher incidence of TNBC in Black women.[14]

Increased BrCa mortality in Black women can be partially attributed to differences in BrCa clinicopathological features,[4,8,15] yet, investigations on potential predictors of aggressive tumor features rather than SES,[8,16-20] are understudied. Although limited, there is evidence shown that stress can cause biological changes among BrCa survivors,[21-23] and further lead to increased BrCa mortality.[23] Therefore, it is reasonable to posit that cumulative stress may be linked to tumor biology. In this study, we hypothesize that unfavorable tumor clinicopathological features, namely invasive tumor behavior, higher tumor grade, larger tumor size, and ER- status are significant consequences of higher cumulative stress using an adapted measure of AL. To our knowledge, this proposed study will be the first study addressing the association between cumulative stress measured by AL and tumor clinicopathological characteristics in Black BrCa survivors.

MATERIALS AND METHODS

Study Sample

As described in Chapter 1, we focused on Black women who were diagnosed with Stage 0, I, II and III BrCa, completed both baseline and F/U-1 interviews and agreed to all medical records release.

Dependent and Independent Variables

Dependent variables (outcomes): Information on tumor characteristics was available from the medical records, and “aggressive tumor characteristics” were defined based on four clinicopathological features listed below:

- Tumor behavior (invasive [Stages I, II and III] vs. non-invasive [Stage 0 or DCIS])
- Tumor grade (poorly differentiated vs. well & moderately differentiated)
- Tumor size (≥2cm vs. <2cm)
- ER status (ER- vs. ER+)

Independent variable (exposures): Cumulative stress measured by AL, the outcome variable in Chapter 1, was used as the main independent variable in this chapter. Specifically, AL measure 1 and AL measure 2 were dichotomized, using a cut-off of 3 points (e.g., 4-8 points= higher AL, 0-3 points=lower AL),[21,24] which was the median score of AL measure 1 and AL measure 2 in this study.

Data Analysis

In addition to sociodemographics, reproductive and clinical characteristics, which were shown in Chapter 1, more descriptive statistics (frequencies and proportions) for tumor clinicopathological characteristics were reported in this study. Bivariate associations between AL with each tumor feature were determined by calculating the odds ratios (ORs) and 95% CIs and the p-values obtained from χ^2 tests. Multivariable logistic regression analyses were applied to build models to report adjusted ORs with 95% CIs. The same covariates mentioned in Chapter 1 were applied to all regression models as potential confounders, and statistically significant confounders ($p<0.05$) were reported in the final models. Sensitivity analysis was also performed to examine the associations of tumor grade, tumor size, ER status, and both AL measure groups

among women with invasive tumors, to address the issue of whether or not including Stage 0 cases in this study would impact the results, given that many characteristics of non-invasive tumors were different from non-metastatic invasive tumors (e.g., many pathology reports did not include ER status for Stage 0 tumors, although it could be done). All analyses were performed using SAS Version 9.4 (SAS institute, Inc., Cary, North Carolina).

RESULTS

The distribution of tumor clinicopathological characteristics among Black breast cancer patients enrolled in WCHFS are shown in Table 1. Among the smaller sample of participants with AL measure 1 estimated (n=229), 37.55% women were diagnosed with Stage II cancer, and 6.55% were diagnosed with Stage III cancer. In addition, 48.6% women had poorly differentiated tumors. In terms of unfavorable receptor status, proportions of ER-, and HER2+ disease were 23.79% and 21.05% in this analytical group. With regard to tumor size, 78 women (34.06%) were found to have tumors ≥2cm. In the larger analytic cohort of women with AL measure 2 (n=409), approximately 45% were diagnosed with Stage II (35.45%) or III tumors (9.29%), almost half were diagnosed with poorly differentiated tumors, approximately 20% had ER- tumors, and about 36% were diagnosed with tumors that were ≥2cm.

Associations between tumor characteristics and AL using logistic regression models are shown in Table 2. Bivariate associations (e.g., univariable models) demonstrated that compared to women with low AL score, those with high AL

score had 87% increased odds of being diagnosed with well/moderately differentiated tumors (OR=1.87, 95% CI: 1.06 to 3.30) among women with AL measure 1. This positive association remained consistent (OR 2.16, 95% CI 1.18 to 3.94) in the multivariable model, controlling for women's age at diagnosis, birthplace, menopausal status, marital status, and family history of BrCa). In terms of AL measure 2, the multivariable analyses suggested that high AL was associated with 60% increased odds of poorly differentiated tumors (OR=1.60, 95% CI 1.02 to 2.51) and 58% increased odds of larger tumor size (OR=1.58, 95% CI 1.01 to 2.46), and age at diagnosis was the strongest confounder among all 5 confounders in adjusted models (data not shown).

DISCUSSION

In this chapter, we investigated the potential consequences of cumulative physiological stress using two adapted measures of AL among Black BrCa survivors, with a primary focus on tumor clinicopathological characteristics. We found that increased odds of observing higher tumor grade were independently associated with higher cumulative stress using AL measure 1 and AL measure 2. Moreover, we also found that higher AL measure 2 was associated with higher odds of large tumor size. Few studies have proposed a potential link between AL and tumor biology,[21,22] indicating that higher AL possibly contributes to aggressive breast cancer clinicopathology.[25] To our knowledge, no previous research has examined the direct relationships between AL and breast cancer clinicopathology, so increased odds of unfavorable tumor clinicopathological

characteristics among Black BrCa survivors experiencing higher AL have never been previously reported. While novel and meaningful, our findings need to be interpreted with caution, given the fact that AL can be computed in various ways (i.e., there is currently no standardized computation method that is widely used by all investigators). Hence, there is a possibility that variation in AL scores might be observed when different biomarkers are collected and utilized from the same study cohort, leading to distinct results with different interpretations.

Evidence-based studies have suggested that cumulative physiological stress may contribute to different chronic diseases,[26,27] and the co-existence of metabolic syndrome related chronic diseases (e.g., hypertension, diabetes, CVD) is common with detrimental impact on BrCa progression and survivorship.[28-33] It has been widely accepted that aggressive tumor characteristics can have a substantive negative impact on BrCa survivorship, however, the biological mechanisms underlying how relevant chronic diseases lead to unfavorable tumor clinicopathological features remain largely unknown. To date, only one published article has discussed the impact of AL on health outcomes in Black women at the cellular level, suggesting that epigenomic changes, namely DNA methylation, alterations on covalent histone modifications, changes in expression of microRNA and long non-coding RNA, play important roles in linking chronic stress and disease,[34] such as TNBC.[25,34] As expected, our study showed that higher AL was significantly associated with higher tumor grade and larger tumor size among Black BrCa survivors, given that tumor grade and tumor size were two important contributors of aggressive tumor biology. Conversely, other

contributors of aggressive tumor clinicopathology, namely invasive tumor behavior and ER- status, were not significantly associated with higher AL as hypothesized. However, they may have been attributed to small samples of Stage III tumors and ER- tumors. More large studies are needed to better elucidate the nature of these associations, and in addition, our future goals include investigating the associations of unfavorable tumor subtypes (e.g. TNBC) and higher AL when the sample size is large enough to make this analysis feasible.

There are some limitations that should be considered. First of all, as mentioned in Chapter 1, this study has a limited statistical power to detect significant associations of interest, particularly for analysis of AL measure 1 with 229 participants only. Secondly, given that many characteristics of invasive tumors (e.g., Stage I, II, III and IV) are different from non-invasive tumors (e.g., Stage 0 or DCIS), using tumor behavior (e.g., invasive vs. non-invasive) as a component to describe tumor clinicopathological feature may be another limitation of the study. There may be an impact of AL on advanced tumor stages (e.g., Stage III and IV), but we don't have enough samples to analyze. Third, receptor status for Stage 0 cases are not always available from pathology reports, thus, including Stage 0 cases in this study may also introduce additional biases. In sensitivity analysis, we re-examined these associations and focused on women with invasive tumors only, and found that a stronger magnitude was observed in the associations between AL and tumor grade among women in the AL measure 1 group, and a similar magnitude yet not statistically significant for

women in the AL measure 2 group. Likewise, although statistically insignificant (p=0.12 in the AL measure 2 group), excluding DCIS cases also led to higher odds of having ER-, which could be driven by some biases (Table 3). Finally, AL can be calculated differently based on data availability with an arbitrary cut-off value to distinguish higher AL from lower AL, therefore, findings reported by this study may not be generalizable to all study samples.

There are also several strengths that should also be noted. First, unlike many BrCa studies in the literature that were primarily based on either self-reported questionnaire data or medical records, we utilized information gathered from both sources. More importantly, if information was available from questionnaire data and medical records, a preferred data source was identified first, and data were requested from the preferred source, which was normally abstracted from medical records. The secondary data source was also utilized if data obtained from the primary source were missing or questionable, thereby increasing our sample size with minimized information bias. Moreover, it is also the first known observational study nested in a large on-going population-based study to evaluate the consequences of cumulative physiological stress with respect to BrCa phenotypes in Black women.

In conclusion, this study contributes to the limited research on consequences of high cumulative physiological stress among Black women diagnosed with BrCa, with a major focus on clinicopathological features. Findings from our research has addressed several gaps in knowledge related to the potential mechanisms involved in the development of aggressive breast cancer

phenotypes among Black women, who are more frequently diagnosed with ER- tumors and those more aggressive features, likely contributing to the observed worse outcomes compared to women in other ethnic groups. Additional research with a focus on molecular mechanisms that explain how AL impacts breast tumors is warranted.

TABLES

Table 1. Breast cancer clinicopathological characteristics among Black breast cancer survivors enrolled in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure 1[a] (n=229)	**Allostatic Load Measure 2[b] (n=409)**
Clinicopathological characteristics	***n (%)***	***n (%)***
Tumor stage		
Stage 0	48 (20.96)	86 (21.03)
Stage I	80 (34.93)	140 (34.23)
Stage II	86 (37.55)	145 (35.45)
Stage III	15 (6.55)	38 (9.29)
Tumor grade		
Well differentiated	33 (15.42)	55 (14.36)
Moderately differentiated	77 (35.98)	137 (35.77)
Poorly differentiated	104 (48.60)	191 (49.87)
ER Status		
ER+	173 (76.21)	314 (77.15)
ER-	54 (23.79)	93 (22.85)
HER2 Status		
HER2+	40 (21.05)	71 (20.94)
HER2-	150 (78.95)	268 (79.06)
Tumor size		
<2cm	151 (65.94)	262 (64.06)
≥2cm	78 (34.06)	147 (35.94)

NOTE: Percentages may not sum to 100 due to rounding. All Stage 0 cases were classified as tumor size <2cm.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
[a] Allostatic Load Measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high density lipoprotein, triglycerides, total cholesterol or low-density lipoprotein, and use of medication to control hypertension, hypercholesterolemia, or diabetes.
[b] Allostatic load measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

Table 2. Univariable and multivariable[a] logistic regression analyses of the associations between high allostatic load[b] and unfavorable breast cancer clinicopathological characteristics among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure 1[c] (High vs. Low) *OR (95% CI)*		**Allostatic Load Measure 2[d] (High vs. Low) *OR (95% CI)***	
	Univariable	**Multivariable**	**Univariable**	**Multivariable**
Tumor behavior: invasive (Stage I, II, & III) vs. non-invasive (Stage 0 or DCIS)				
Allostatic load				
Low (0-3 points)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8 points)	1.09 (0.56,2.14)	1.23 (0.62,2.47)	1.02 (0.63,1.64)	1.20 (0.72,1.99)
	p=0.7936	p=0.5554	p=0.9477	p=0.4913
Tumor grade: poorly differentiated vs. well & moderately differentiated				
Allostatic load				
Low (0-3 points)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8 points)	**1.87 (1.06,3.30)**	**2.16 (1.18,3.94)**	1.15 (0.77,1.71)	**1.60 (1.02,2.51)**
	p=0.0313	**p=0.0127**	p=0.5080	**p=0.0391**
Tumor size: ≥2cm vs. <2cm				
Allostatic load				
Low (0-3 points)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8 points)	0.90 (0.51,1.60)	1.00 (0.55,1.84)	1.22 (0.81,1.83)	**1.58 (1.01,2.46)**
	p=0.7150	p=0.9910	p=0.3418	**p=0.0434**
ER status: ER- vs. ER+				
Allostatic load				
Low (0-3 points)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8 points)	1.17 (0.62,2.20)	1.12 (0.59,2.16)	1.24 (0.78,1.98)	1.23 (0.75,2.01)
	p=0.6355	p=0.7272	p=0.3581	p=0.4094

NOTE: All Stage 0 cases were classified as tumor size <2cm. Bold values indicate statistical significance. Abbreviations: ER, estrogen receptor.

[a] The following confounders were included in the multivariable-adjusted regression analyses: 1) age at diagnosis; 2) birthplace; 3) marital status; 4) menopausal status; 5) family history of BrCa.

[b] The median allostatic load score among Black WCFHS participants was 3. Thus, 3 was used as the cut-off point to dichotomize the allostatic load variable.

[c] Allostatic Load Measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high density lipoprotein, triglycerides, total cholesterol or low-density lipoprotein, and use of medication to control hypertension, hypercholesterolemia, or diabetes.
[d] Allostatic load measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes

Table 3. Sensitivity analysis. Multivariable-adjusted[a] logistic regression analyses of the associations between high cumulative stress[b] and unfavorable breast cancer clinicopathological characteristics among Black women with invasive breast cancer in the Women's Circle of Health Study (WCHFS), using two allostatic load computational methods

	Allostatic Load Measure 1[c,d] (n=181) *OR (95% CI)*	**Allostatic Load Measure 2[e,f] (n=323)** *OR (95% CI)*
Tumor grade: poorly differentiated vs. well & moderately differentiated		
Allostatic load		
Low (0-3 points)	1.00 (Referent)	1.00 (Referent)
High (4-8 points)	**2.49 (1.28,4.85) p=0.0074**	**1.66 (1.02,2.72) p=0.0425**
Tumor size: ≥2cm vs. <2cm		
Allostatic load		
Low (0-3 points)	1.00 (Referent)	1.00 (Referent)
High (4-8 points)	0.93 (0.49,1.79) p=0.3760	0.93 (0.49,1.79) p=0.3760
ER status: ER- vs. ER+		
Allostatic load		
Low (0-3 points)	1.00 (Referent)	1.00 (Referent)
High (4-8 points)	1.27 (0.63, 2.57) p=0.5062	1.52 (0.89,2.57) p=0.1228

NOTE: Bold values indicate statistical significance. Abbreviations: ER, estrogen receptor.

[a] The following confounders were included in the multivariable-adjusted regression analyses: 1) age at diagnosis; 2) birthplace; 3) marital status; 4) menopausal status; 5) family history of breast cancer.

[b] The median allostatic load score among Black WCHFS participants was 3. Thus, 3 was used as the cut-off point to dichotomize the allostatic load variable.

[c] Allostatic Load Measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high density lipoprotein, triglycerides, total cholesterol, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[d] Includes Black WCHFS participants who were diagnosed with Stage I, II and III cancer in the allostatic load measure 1 group (n=181).

[e] Allostatic Load Measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[f] Includes Black WCHFS participants who were diagnosed with Stage I, II and III cancer in the allostatic load measure 2 group (n=323).

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ASSOCIATIONS OF QUALITY OF LIFE AND ALLOSTATIC LOAD AMONG BLACK BREAST CANCER SURVIVORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

By

CATHLEEN Y. XING

Chapter 3 of 3 of a dissertation entitled

PREDICTORS AND CONSEQUENCES OF CUMULATIVE STRESS AMONG BLACK BREAST CANCER SURVIVORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

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Written under the direction of

Adana A. M. Llanos, PhD, MPH

ABSTRACT OF CHAPTER 3 OF 3

Associations of Quality of Life and Allostatic Load Among Black Breast Cancer Survivors in the Women's Circle of Health Follow-Up Study

by CATHLEEN Y. XING

Dissertation Director:

Adana A.M. Llanos, PhD, MPH

Background: In the U.S., Black women tend to have higher cumulative physiological stress compared with women of other races/ethnicities, which may contribute to poor health-related quality of life (QoL) following a diagnosis of breast cancer (BrCa). While substantial QoL studies have been conducted among BrCa survivors, few have examined this hypothesis among Black women. The purpose of this study was to examine the association of allostatic load (AL; as a measure of cumulative physiological stress) and QoL among Black BrCa survivors.

Methods: In a sample of 409 Black women with non-metastatic BrCa enrolled in the Women's Circle of Health Follow-Up Study (WCHFS), pre-diagnostic AL was computed using two methods: AL measure 1 (lipid profile-based measure) and AL measure 2 (inflammatory index-based measure), as described in Chapters 1 and 2 of this study. QoL measures were selected from the validated Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) instrument, and 5

subscale scores (presented by physical well-being, social/family well-being, emotional well-being, functional well-being, and BrCa-specific scale) and 3 derived total scores (presented by trial outcome index, Functional Assessment of Cancer Therapy-General [FACT-G] and overall FACT-B) were calculated using the standard FACT-B scoring guidelines. Multivariable logistic regression models were used to assess the associations between the two AL measures and QoL.

Results: Among women with AL measure 2, higher AL was found to be a significant predictor of poorer physical well-being (OR=1.60; 95% CI: 1.05, 2.44), poorer functional well-being (OR=1.63; 95% CI: 1.07, 2.49), and lower FACT-G (OR=1.71; 95% CI: 1.12, 2.60) scores. No significant associations were observed for any FACT-B subscale scores, derived total scores with AL measure 1.

Conclusions: These findings suggest that poorer QoL measured by physical well-being, functional well-being and FACT-G scales are potential consequences of higher AL among Black BrCa survivors. Healthcare practitioners should consider these findings when developing intervention strategies to improve QoL among Black BrCa survivors.

ASSOCIATIONS OF QUALITY OF LIFE AND ALLOSTATIC LOAD AMONG BLACK BREAST CANCER SURVIVORS IN THE WOMEN'S CIRCLE OF HEALTH FOLLOW-UP STUDY

INTRODUCTION

Health-related quality of life (QoL) is referred to as perceived physical and mental health over time among individuals and/or groups.[1] In BrCa studies, mental distress is one particularly important component of QoL among BrCa survivors.[2-7] Although many QoL studies have been conducted among cancer survivors, fewer studies have focused on Black women with BrCa, who are frequently diagnosed at younger age with more aggressive tumor features,[7,8] suggesting a greater need for evaluating QoL in Black BrCa survivors.[4]

Mental distress is one of the most frequently reported QoL components among BrCa survivors,[9-11] and it is often related to fear of BrCa recurrence,[12,13] worry about other adverse health outcomes,[14] and concern about whether a family member might develop BrCa someday.[15] One study has shown that nearly one third of all BrCa survivors have reported significant depressive symptoms.[10] Other studies have demonstrated that approximately 30%–50% of BrCa survivors have experienced some psychosocial distress, and the odds of having mental distress in women with BrCa is much higher compared to the general population.[16-19] In addition to mental and psychological distress, many BrCa survivors are continuously affected by other QoL-related factors suggested by popular QoL instruments for BrCa survivors (e.g., Functional Assessment of

Cancer Therapy [FACT-B]) as well,[20] such as pain,[21-24] fatigue or lack of energy,[21,23-26] poor sexual function,[21,24] and sleep problems.[4,21,27-33]

There are some available data on the impact of AL on QoL measures in cancer survivors, which have suggested interventional strategies to improve QoL,[34,35] with very limited research focused on the relationship of AL with QoL among Black BrCa survivors. With regard to the psychological health component, dysregulation of the HPA axis is sensitive to psychological stress, and further, abnormal or flattened cortisol rhythmicity is positively associated with perceived psychological and mental distress in BrCa survivors.[36] Pain and sleep quality are both important QoL indicators among BrCa survivors. Pain has detrimental effects on homeostasis, and it has been suggested to be a homeostatic emotion.[37,38] Pain is also associated with various stress hormones (e.g., cortisol and epinephrine),[39] which can trigger a complex neuroendocrine pathway and further activate the HPA-axis and sympathetic nervous activity.[40,41] Similarly, low QoL measures reported by poor sleep quality can be viewed as one of the major consequences of cumulative stress.[42]

To our knowledge, only one study[43] has examined the association between cumulative stress measured by AL, with QoL. This study focused on depressive symptoms and reported null results.[43] Another study thoroughly examined the associations of AL and QoL measures with respect to sleep problems.[35] Both studies utilized NHANES data and highlighted the need for more research among racial/ethnic minority groups.[35,43] However, no previous study has comprehensively addressed the relationship between AL and QoL using a

validated instrument which targets cancer survivors in specific. Such research is particularly important in Black BrCa survivors, who are generally more susceptible to higher AL[44,45] and lower QoL.[46-52] In this study, we hypothesize that poorer QoL measured by FACT-B were significant consequences of high AL among Black BrCa survivors in WCHFS. Findings from this study will address these gaps in knowledge.

MATERIALS AND METHODS

Study Sample

As described in Chapters 1 and 2, we focused on Black women who were diagnosed with Stage 0, I, II and III BrCa, completed both baseline and F/U-1 interviews and agreed to medical records release from January 2014 to August 2018.

Dependent and Independent Variables

Dependent (outcome) variables: QoL measures were selected from the FACT-B questionnaire. FACT-B measured BrCa-specific QoL, which was derived and modified based on the popular Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire in 1997.[53] The FACT-B questionnaire is a well-validated instrument with high reliability,[53] with a total of 37 FACT-B questions grouped into 5 subscales according to the FACT-B scoring guidelines, version 4 (Appendix Table 1). The 5 subscales have a range of scores as follows:

- Physical well-being (PWB): score range: 0-28
- Social & family well-being (SFWB): score range: 0-28

- Emotional well-being (EWB): score range: 0-24
- Functional well-being (FWB): score range 0-28
- Breast cancer-specific scale (BCS): score range: 0-40

The standard FACT-B scoring method was used in this study. First of all, each FACT-B item-specific question had a score value of 0 to 4, and questions were scored so that a higher score indicated a better QoL. Positively written questions were scored as not at all (0 point), a little bit (1 point), somewhat (2 points), quite a bit (3 points), and very much (4 points). Alternatively, negatively written questions were scored as very much (0 point), quite a bit (1 point), somewhat (2 points), a little bit (3 points), and not at all (4 points). After all necessary score reversals were performed, 5 subscale scores were calculated by first multiplying the sum of the item-specific scores by the number of questions in the subscale, then dividing by the number of questions answered in the subscale. A question was considered as “not answered” if a woman indicated that the question was “not applicable” and the corresponding subscale score might be prorated if 50% of more questions in one subscale were answered.

In addition to 5 subscale scores, the total scores were derived by adding specific subscale scores according to the FACT-B scoring guidelines, version 4 (Appendix Table 1), and 3 derived total scores were defined as follows:

- Trial outcome index (TOI) is a QoL score which is especially useful among cancer survivors who underwent chemotherapy. Given that more than half of WCHS participants underwent chemotherapy, TOI was an appropriate

variable to be included in the analysis. The TOI score was derived by adding subscale scores from physical well-being, functional well-being and BrCa-specific scale (score range: 0-96).

- FACT-G is a general QoL measure applicable to all cancer patients, and it was calculated by the sum of physical well-being subscale score, social & family well-being subscale score, emotional well-being subscale score, and functional well-being subscale score (score range: 0-108).
- FACT-B is a QoL measure which targets female BrCa survivors in particular, and it is defined as the sum of the FACT-G score and the BrCa-specific scale subscale score (score range: 0-148).

Prorating FACT-G and FACT-B scores is also permitted as long as overall item response rate was 80% or higher. Ultimately, given that the FACT-B data in WCHFS were highly skewed, all QoL measures (e.g., 5 subscale scores and 3 total scores derived from subscale scores) were initially calculated continuously, then further dichotomized using the median as the cut-off (1 = higher QoL, 0 = lower QoL) in order to perform appropriate data analysis.

Independent (exposure) variables: cumulative stress using an adapted measure of AL, the outcome variable in Chapter 1 and the main exposure of interest in Chapter 2, was used as the main independent (exposure) variable in this Chapter. AL measure 1 and AL measure were dichotomized using a cut-off of >3 points (e.g., 4-8 points= higher AL, 0-3 points=lower AL),[45,54] which was the median score of AL measure 1 and AL measure 2 in this study.

Data Analysis

In addition to sociodemographics, reproductive and clinical characteristics which have been shown in Chapter 1, descriptive statistics with respect to all FACT-B variables (means and standard deviations) for all 37 item-specific questions, 5 subscale scores, and 3 derived total scores were reported in this chapter among women with AL measure 1 and AL measure 2 separately. Frequencies and proportions of dichotomized FACT-B subscale scores and derived total scores were also described. Bivariate associations using unadjusted logistic regression models of the same key predictor variable (e.g., AL measure 1 and AL measure 2) with all 8 QoL measures evaluated by the FACT-B instrument were determined by calculating the ORs and 95% CIs and the p-values obtained from χ^2 tests. Multivariate logistic regression analyses were used to build models to report adjusted ORs with 95% CIs. The same co-variables mentioned in Chapters 1 and 2 (age at diagnosis, birthplace, marital status, menopausal status, and family history of BrCa) were included in all multivariable logistic regression models as potential confounders. All analyses were performed using SAS Version 9.4 (SAS institute, Inc., Cary, North Carolina).

RESULTS

The distributions of the QoL measures presented by item-specific scores and grouped by subscales among women included in the analytic cohort are shown in Table 1. More than half of the item-specific questions listed in the physical well-being and social & family well-being subscales, and all item-specific

questions listed in the emotional well-being subscale had mean QoL scores above 3, indicating that most women responded “quite a bit” or “very much” to these questions. Among all 37 item-specific questions, the question about “losing hope” in the emotional well-being subscale had the highest item-specific QoL score in both AL measure groups, which was 3.79±0.69 among the 229 women with AL measure 1, and 3.77±0.70 among the 409 women with AL measure 2. Conversely, a majority of item-specific questions in the functional well-being and BrCa-specific scale subscales had average scores between 2 and 3, and remarkably lower item-specific scores were observed in the BrCa-specific subscale. Specifically, a BrCa-specific scale question regarding whether a woman had certain painful parts had the lowest item-specific score among all 37 item-specific questions presented by FACT-B, with a score of 2.29±1.34 among women in the AL measure 1 group, and 2.27±1.34 for women in the larger AL measure 2 group.

Table 2 depicts descriptive statistics for all calculated subscale scores and derived total scores presented as continuous variables. Among subscales with the same score range (e.g., physical well-being, social & family well-being, and functional well-being), the functional well-being subscale had a lower average score compared with physical well-being and social & family well-being; a similarly low score in the functional well-being subscale was observed among women in both AL measure groups. In addition to the continuous scales mentioned above, all 5 subscale scores and 3 derived total scores were further dichotomized using median scores of each corresponding variable as cut-offs,

and frequencies and proportions of all dichotomized FACT-B variables were reported (Table 2). We found that 57.71% of the sample reported a higher QoL measure assessed by the physical well-being subscale, while 50.22% reported a higher QoL represented by emotional well-being among women in the AL measure 1 group. For women in the AL measure 2 group, 233 (57.39%) indicated a higher QoL measured by emotional well-being, compared to 205 (50.49%) who reported a higher QoL measure evaluated by total outcome index.

Table 3 presents unadjusted and multivariable-adjusted logistic regression analyses of the associations between higher AL with lower QoL assessed by physical well-being, social & family well-being, emotional well-being, functional well-being, BrCa-specific scale, total outcome index, FACT-G and FACT-B. In the adjusted analysis, we found that with respect to the subscale QoL measures, those with higher AL measure 2 had 60% increased odds of reporting lower physical well-being (OR=1.60, 95% CI: 1.05 to 2.44), and 63% increased odds of reporting lower functional well-being (OR=1.63, 95% CI: 1.07 to 2.49). Menopausal status was shown to be a stronger confounder among all 5 confounders included in the models of physical well-being and AL measure 2 (data not shown). In terms of derived total scores, women with higher AL measure 2 had 71% increased odds of having lower FACT-G score (OR=1.71, 95% CI: 1.12 to 2.60). No significant associations were observed for AL measure 1. Although inverse associations between AL and QoL with respect to social & family well-being, emotional well-being, BrCa-specific scale, total outcome index,

and FACT-B were also suggested, these associations did not reach statistical significance among women in neither AL measure groups.

DISCUSSION

Through this assessment of the association between AL (as a measure of cumulative physiological stress) and QoL among Black BrCa survivors enrolled in WCHFS, we found that QoL concerns reported among Black WCHFS participants were generally related to pain, concerns related to sex, low energy and fatigue, mental distress, and poor sleep quality. These findings were consistent with the current literature.[4,15,21-32,55] Second, our results also demonstrated that the proportions of item-specific questions with QoL scores of 2.50 or lower were remarkably higher in the BrCa-specific scale subscale compared to the proportions of item-specific questions that were scored 2.50 or lower with all other 4 subscales. This finding suggests that most Black BrCa survivors in this study were satisfied with general cancer-related QoL measures (e.g., physical well-being, social & family well-being, emotional well-being and functional well-being), but not with BrCa-specific QoL measures. Given that questions listed in the BrCa-specific subscale were specifically designed for BrCa survivors, but not other cancer survivors, our findings might suggest that targeted intervention strategies in order to improve overall QoL in Black BrCa survivors are needed.

To date, most QoL research in BrCa survivors has focused on mental health (e.g., depression, anxiety, perceived psychological stress)[2-7] and sleep problems

[35] using validated instruments, such as Center for Epidemiological Studies Depression Scale (CES-D), Hospital Anxiety and Depression Scale (HADS), and Pittsburgh Sleep Quality Index (PSQI). Unlike other validated QoL instruments, FACT-B is specially designed for BrCa survivors because it is more sensitive in capturing BrCa related changes.[53] Hence, FACT-B seems to be the most appropriate QoL instrument for use in WCHFS because none of the other validated instruments comprehensively addresses QoL concerns among BrCa survivors. Observational studies using FACT-B scales have shown that Black BrCa survivors were more likely to experience worse physical conditions[2,50,56] and poorer social and family wellness.[56] In contrast, previous evidence also suggested that Black BrCa survivors tend to report better emotional well-being compared to women in other racial/ethnic groups in the U.S. in general.[56,57] In our study, the average score for all item-specific questions in emotional well-being were scored above 3.00, which was suggestive of higher QoL related to emotional well-being among Black BrCa survivors and consistent with the literature. However, it is worth noting that the emotional wellness for most U.S. BrCa survivors also declines over time.[58] Thus, it is possible to observe a lowering of emotional well-being scores among WCHFS participants once women have completed more annual F/U interviews.

Our findings showed increased odds of lower physical and functional well-being among women with higher AL, and these findings could be explained by different mechanisms. First, sleep quality was one component in the functional well-being subscale, and poor sleep quality has been frequently reported by

BrCa survivors.[4,21,27-33] Circadian disruption caused by poor sleep quality could have detrimental effects on overall QoL in BrCa survivors.[33] In addition, circadian disruption caused by low sleep quality may disturb normal neurophysiological functions, and impaired neurophysiological functions can affect cumulative stress by increasing pro-inflammatory cytokines, abnormal insulin and cortisol concentrations (e.g., stressors that are associated with AL),[60] and further lead to poorer QoL.[60,61] We also observed a suggestion of an inverse association between AL and QoL measured by the BrCa-specific scale subscale, although this finding did not reach statistical significance. BrCa-specific scale was the only subscale with a specific focus on BrCa-related concerns (e.g., femininity, arm/shoulder pain, and sexual attractiveness after the treatment), thus, higher AL was originally hypothesized to show a stronger impact on lower QoL addressed by the BrCa-specific scale subscale (compared with causal other FACT-G subscales) given the study sample. Also, the descriptive data showed that many questions related to BrCa-specific concerns had remarkably lower scores compared with questions in other FACT-G subscales, suggesting a greater variability in BrCa-specific scale subscale among WCHFS participants. No significant associations were observed between higher AL and lower BrCa-specific subscale score or total FACT-B score among WCHFS participants, which might be due to a small sample size in this study. Likewise, this study also demonstrated a lack of significant association between QoL measured by total outcome index and AL score, and the relatively small sample size of women (e.g., 118 women with AL measure 1 and 210 women with AL measure 2) who

had chemotherapy could be the main cause. Okuma et al. concluded that although total outcome index primarily targets women who have had chemotherapy to treat BrCa, this index has a limited ability to evaluate QoL among all BrCa survivors.[62]

Strong spiritual and social support from church families may have positive effects on social and family wellness and emotional wellness among Black BrCa survivors; however, spiritual and social support is unlikely to impact most BrCa specific concerns, such as pain, swollen arms, hair loss, and sexual attractiveness. We hypothesize that differences in QoL scores in FACT-B subscales observed in this study may be explained by strong religious and spiritual beliefs among Black women. Ashing-Giwa et al. suggested that church is the primary source of support among Black BrCa survivors, who usually hold stronger religious and spiritual beliefs compared with other U.S. women.[63] Higher AL was shown to be a significant predictor of poorer functional wellness in this study, and similar results were observed for both AL measures. Furthermore, we also found positive, yet not statistically significant, associations between higher AL with lower social and family well-being, emotional well-being, BrCa-specific scale, total outcome index, and FACT-B. These findings may be explained by a limited statistical power. Although women's QoL was assessed by the validated FACT-B instrument, findings from this study should be interpreted with caution because only 409 Black women with BrCa enrolled in WCHFS were included in this analysis, so it is unclear whether the results are generalizable to all Black women with BrCa.

The use of a dichotomized version of all FACT-B subscales and derived total scores in the examination of consequences of AL is one of the major limitations in this study. As described, FACT-B is a validated instrument with a standardized scoring system, and all FACT-B variables are generally used as continuous variables in many published studies between 2009 to 2018.[33,57,58,62,64-70] For our study, using binary FACT-B outcome variables was preferred due to highly skewed QoL data reported by WCHFS participants. However, dichotomizing FACT-B variables in this study potentially makes it hard to compare our results with other studies, given that the definition of "poor QoL" likely differs by statistical method, even if all studies followed the same scoring guidelines. In reality, most QoL data that are indicative of high QoL are skewed, therefore, the fact of having highly left-skewed FACT-B measures in our study is consistent with previously published BrCa studies.[57,70-72] The reasons for observing left-skewed QoL data in WCHFS are likely to be multifactorial, and one possible explanation is that women who were very sick were unlikely to participate WCHFS, or unable to stay focused and provide accurate and reliable responses while being interviewed. Therefore, it is reasonable to posit that women who have participated in WCHFS were generally healthier (than those who did not participate) and therefore more satisfied with their QoL as BrCa survivors. Additionally, personal questions (e.g., about sex and partner) were used to assess some aspects of QoL, making this study prone to reporting bias. One FACT-B question related to social and family wellness specifically asked about whether a woman was satisfied with her sex life, and in WCHFS,

approximately 20% women preferred not to answer this question, or indicated that this question was not applicable. Thus, about 80% women have responded to the sex life related question, however, the responses provided by these women might be questionable. Regardless of whether women responded to the question related to their sex life or not, almost all participants indicated that they felt close to their partners, which was another personal question that could be potentially influenced by the presence or absence of a “partner” and thus could contribute to issues with how women responded to the aforementioned sex life-related question.

Despite these limitations, the major strength of this study was that it is the first to have examined lower QoL as a potential consequence of higher AL among Black women with BrCa, who tend to experience higher cumulative physiological stress[44,45] and lower health-related QoL.[46-52] Using FACT-B for QoL assessment among WCHFS participants is also major strength of this study. FACT-B is the only validated instrument to measure QoL in women with BrCa, hence, factors that mainly affect BrCa survivors were accounted for. As WCHFS is an on-going, longitudinal population-based study with detailed data collected through medical records, and interviewer-administered questionnaire data at multiple time points, so if certain information is missing or questionable from one data source, it is still possible to obtain relevant data from other sources, so the proportions of missing data may be minimized.

In summary, findings from this chapter contributes to the limited research on the consequences of higher AL (as a measure of cumulative physiological stress)

among Black BrCa survivors, with a major focus on QoL. While not all FACT-B subscales were shown to be associated with AL, the significant inverse relationship between higher AL and poorer physical well-being, functional well-being, and FACT-G scores might be useful in explaining some of the causes of poorer QoL among Black BrCa survivors in general. Larger studies examining the impacts of AL on QoL, particularly among Black women with BrCa is needed to clarify the findings reported herein.

TABLES

Table 1. Item-specific quality of life (QoL) scores assessed by Functional Assessment of Cancer Therapy (FACT-B) instrument[a] among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure 1[b]	Allostatic Load Measure 2[c]
FACT-B Instrument Subscales	***mean±SD***	***mean±SD***
Physical Well-Being (PWB)		
PWB1: lack of energy	2.42±1.19	2.42±1.21
PWB2: have nausea	3.73±0.59	3.68±0.72
PWB3: meeting family needs	3.36±1.06	3.38±1.06
PWB4: have pain	2.68±1.31	2.70±1.32
PWB5: bothered by side effects	3.03±1.32	2.99±1.34
PWB6: feel ill	3.49±0.94	3.47±0.95
PWB7: spend time in bed	3.41±1.06	3.40±1.05
Social/ Family Well-Being (SFWB)		
SFWB1: close to friends	2.96±1.19	2.98±1.17
SFWB2: get emotional support	3.47±0.88	3.40±0.97
SFWB3: supportive friends	3.26±1.06	3.21±1.10
SFWB4: illness accepted by family	3.67±0.77	3.67±0.75
SFWB5: family communication	3.54±0.95	3.50±0.98
SFWB6: feel close to partner	3.50±1.00	3.49±0.98
SFWB7: satisfied with sex life	2.51±1.62	2.46±1.56
Emotional Well-Being (EWB)		
EWB1: feed sad	3.05±1.13	3.05±1.16
EWB2: satisfied with coping strategy	3.25±1.02	3.16±1.10
EWB3: lose hope	3.79±0.69	3.77±0.70
EWB4: feel nervous	3.39±0.94	3.36±0.98
EWB5: worry about dying	3.45±0.95	3.41±1.01
EWB6: worry about worsening condition	3.33±1.00	3.26±1.03
Functional Well-Being (FWB)		
FWB1: able to work	3.07±1.25	3.12±1.23
FWB2: fulfilling work	2.92±1.25	2.84±1.26
FWB3: able to enjoy life	3.27±0.96	3.29±0.95
FWB4: have accepted illness	3.62±0.87	3.56±0.90
FWB5: good sleep quality	2.44±1.37	2.44±1.38
FWB6: enjoy fun things	2.81±1.27	2.83±1.28
FWB7: content with QoL	2.78±1.28	2.75±1.30
Breast Cancer-Specific Scale (BCS)		
BCS1: shortness of breath	3.30±0.97	3.32±1.02
BCS2: self-conscious about dressing	2.98±1.46	2.93±1.44
BCS3: swollen or tender arms	3.24±1.23	3.28±1.19
BCS4: feel sexually attractive	2.33±1.40	2.33±1.44
BCS5: bothered by hair loss	2.99±1.47	3.12±1.40
BCS6: worry about family members	2.43±1.41	2.37±1.44
BCS7: worry about the effect of stress	2.52±1.44	2.39±1.48
BCS8: bothered by weight change	2.34±1.57	2.34±1.57
BCS9: feel like a woman	3.28±1.02	3.20±1.08
BCS10: have certain painful parts	2.29±1.34	2.27±1.34

NOTE: Percentages may not sum to 100 due to rounding.

[a] See Appendix Table 1 for original questions and subscales. All items were scored so that a higher score indicated a higher QoL measure.

[b] Allostatic Load Measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high density lipoprotein, triglycerides, total cholesterol, and use of medication to control hypertension, hypercholesterolemia, or diabetes.
[c] Allostatic Load Measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

Table 2. Distributions of subscale and derived total scores[a] assessed by Functional Assessment of Cancer Therapy (FACT-B) instrument among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure 1[b]	**Allostatic Load Measure 2[c]**
Continuous variables	***mean±SD***	***mean±SD***
PWB subscale score (0-28)	22.10±5.10	22.03±5.23
SFWB subscale score (0-28)	23.04±4.79	22.82±5.02
EWB subscale score (0-24)	20.27±3.94	20.01±4.21
FWB subscale score (0-28)	20.92±5.87	20.80±6.06
BCS subscale score (0-40)	27.73±7.01	27.56±7.17
Derived total TOI score (0-96)	70.76±15.65	70.39±16.04
Derived total FACT-G score (0-108)	86.33±15.81	85.80±16.63
Derived total FACT-B score (0-148)	114.06±21.43	113.22±22.38
Categorical variables[d]	***n (%)***	***n (%)***
PWB subscale (0-28)		
High (≥23)	131 (57.71)	229 (56.54)
Low (<23)	96 (42.29)	176 (43.46)
SFWB subscale (0-28)		
High (≥24)	120 (52.86)	215 (52.96)
Low (<24)	107 (47.14)	191 (47.04)
EWB subscale (0-24)		
High (≥22 for AL 1 and ≥21 for AL 2)	114 (50.22)	233 (57.39)
Low (<22 for AL 1 and <21 for AL 2)	113 (49.78)	173 (42.61)
FWB subscale (0-28)		
High (≥22)	122 (53.74)	221 (54.43)
Low (<22)	105 (46.26)	185 (45.57)
BCS subscale (0-40)		
High (≥28)	122 (53.74)	220 (54.19)
Low (<28)	105 (46.26)	186 (45.81)
Derived total TOI (0-96)		
High (≥73)	117 (51.54)	205 (50.49)
Low (<73)	110 (48.46)	201 (49.51)
Derived total FACT-G (0-108)		
High (≥89)	117 (51.54)	209 (51.60)
Low (<89)	110 (48.46)	196 (48.40)
Derived total FACT-B (0-148)		
High (≥117)	115 (50.66)	207 (50.99)
Low (<117)	112 (49.34)	199 (49.01)

NOTE: Percentages may not sum to 100 due to rounding.

[a] See Appendix Table 1 for original subscales and derived total score formulas. All items were scored so that a higher score indicated a higher QoL measure. Prorating a subscale score was acceptable if 50% or more items in a particular subscale were answered. FACT-G and FACT-B scores were calculated if overall item response rate was 80% or higher.

[b] Allostatic Load Measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high density lipoprotein, triglycerides, total cholesterol, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[c] Allostatic Load Measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[d] Variables were dichotomized by using median scores as cut-offs.

Table 3. Univariable and multivariable[a] logistic regression analyses of the associations between high allostatic load[b] and low quality of life (QoL) measured by FACT-B instrument[c] among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

	Allostatic Load Measure1[d]		**Allostatic Load Measure 2[e]**	
	OR (95% CI)		***OR (95% CI)***	
Subscales and derived total scores[f]	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**
PWB subscale: Low (<23) vs. High (≥23)				
Allostatic load				
Low (0-3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8)	0.97 (0.56,1.68)	0.99 (0.56,1.76)	1.40 (0.95, 2.09)	**1.60 (1.05, 2.44)**
	P = 0.9081	P = 0.9754	P = 0.2203	**P = 0.0279**
SFWB subscale: Low (<24) vs. High (≥24)				
Allostatic load				
Low (0-3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8)	1.24 (0.72, 2.14)	1.28 (0.73, 2.24)	1.08 (0.73,1.59)	1.09 (0.72,1.66)
	P = 0.4410	P = 0.3991	P = 0.7113	P = 0.6765
EWB subscale: Low (<22 for AL 1; <21 for AL 2) vs. High (≥22 for AL 1; ≥21 for AL 2)				
Allostatic load				
Low (0-3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8)	0.90 (0.52,1.56)	1.03 (0.58,1.83)	0.96 (0.64,1.42)	1.27 (0.82,1.95)
	P = 0.7119	P = 0.9324	P = 0.8203	P = 0.2823
FWB subscale: Low (<22) vs. High (≥22)				
Allostatic load				
Low (0-3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8)	1.53 (0.88, 2.65)	1.53 (0.87, 2.70)	**1.59 (1.07, 2.36)**	**1.63 (1.07, 2.49)**
	P = 0.1281	P = 0.1430	**P = 0.0212**	**P = 0.0266**
BCS subscale: Low (<28) vs. High (≥28)				
Allostatic load				
Low (0-3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8)	1.31 (0.76, 2.27)	1.51 (0.85, 2.68)	1.13 (0.76,1.68)	1.40 (0.92, 2.15)
	P = 0.3343	P = 0.1575	P = 0.5372	P = 0.1208

Table 3 (Cont'd). Univariable and multivariable[a] logistic regression analyses of the associations between high allostatic load[b] and low quality of life (QoL) measured by FACT-B instrument[c] among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), using two allostatic load computational methods.

Derived total TOI: Low (<73) vs. High (≥73)				
Allostatic load				
Low (0-3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8)	1.24 (0.72, 2.13)	1.26 (0.71, 2.23)	1.29 (0.87,1.91)	1.17 (0.70,1.93)
	P = 0.4489	P = 0.4244	P = 0.2027	P = 0.0977
Derived total FACT-G: Low (<89) vs. High (≥89)				
Allostatic load				
Low (0-3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8)	1.34 (0.77, 2.31)	1.42 (0.81, 2.49)	**1.52 (1.02,2.25)**	**1.71 (1.12, 2.60)**
	P = 0.3004	P = 0.2277	**P = 0.0378**	**P = 0.0123**
Derived total FACT-B: Low (<117) vs. High (≥117)				
Allostatic load				
Low (0-3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4-8)	1.08 (0.63,1.87)	1.19 (0.68, 2.09)	1.19 (0.80,1.76)	1.41 (0.92, 2.14)
	P = 0.7758	P = 0.5480	P = 0.3926	P = 0.1177

NOTE: Bold values indicated statistical significance. Abbreviations: FACT-G, Functional Assessment of Cancer Therapy-General; FACT-B, Functional Assessment of Cancer Therapy-Breast Cancer.

[a] The following confounders were included in the multivariable analysis: 1) age at diagnosis, 2) birthplace, 3) marital status, 4) menopausal status and 5) family history of breast cancer.

[b] 3 point was the median allostatic load score among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS) and thus was used as the cut-off point to dichotomize the variable.

[c] See Appendix Table 1 for original subscales and derived total score formulas. All items were scored so that a higher score indicated a higher QoL measure. Prorating a subscale score was acceptable if 50% or more items in a particular subscale were answered. FACT-G and FACT-B scores were calculated if overall item response rate was 80% or higher. All FACT-B variables were dichotomized by using median scores as cut-offs.

[d] Allostatic load measure 1 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, high density lipoprotein, triglycerides, total cholesterol, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[e] Allostatic load measure 2 was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

[f] Variables were dichotomized by using median scores as cut-offs.

Appendix Table 1. Validated items measuring quality of life (QoL) using Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) instrument among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS).

Subscales	
Physical Well-Being (PWB)	
PWB1[a]	You have a lack of energy
PWB2[a]	You have nausea
PWB3[a]	You have trouble meeting the needs of your family
PWB4[a]	You have pain
PWB5[a]	You are bothered by side effects of treatment
PWB6[a]	You feel ill
PWB7[a]	You are forced to spend time in bed
Social & Family Well-Being (SFWB)	
SFWB1[b]	You feel close to your friends
SFWB2[b]	You get emotional support from your family
SFWB3[b]	You get support from your friends
SFWB4[b]	Your family has accepted your illness
SFWB5[b]	You are satisfied with family communication about your illness
SFWB6[b]	You feel close to your partner (or the person who is your main support)
SFWB7[b]	You are satisfied with your sex life
Emotional Well-Being (EWB)	
EWB1[a]	You feel sad
EWB2[b]	You are satisfied with how you are coping with your illness
EWB3[a]	You are losing hope in the fight against your illness
EWB4[a]	You feel nervous
EWB5[a]	You worry about dying
EWB6[a]	You worry that your condition will get worse
Functional Well-Being (FWB)	
FWB1[b]	You are able to work (include work at home)
FWB2[b]	Your work (include work at home) is fulfilling
FWB3[b]	You are able to enjoy life
FWB4[b]	You have accepted your illness
FWB5[b]	You are sleeping well
FWB6[b]	You are enjoying things you usually do for fun
FWB7[b]	You are content with the quality of your life right now
Breast Cancer Specific Scale (BCS)	
BCS1[a]	You have been short of breath
BCS2[a]	You are self-conscious about the way you dress
BCS3[a]	One or both of your arms are swollen or tender
BCS4[b]	You feel sexually attractive
BCS5[a]	You are bothered by hair loss

BCS6[a]	You worry that other family members might someday get the same illness
BCS7[a]	You worry about the effect of stress on your illness
BCS8[a]	You are bothered by a change in weight
BCS9[b]	You are able to feel like a woman
BCS10[a]	You have certain parts of your body where you experience pain
Derived total scores	
TOI	Sum of PWB, FWB and BCS subscale scores (24 items)
FACT-G[c]	Sum of PWB, SFWB, EWB, and FWB subscale scores (27 items)
FACT-B[c]	Sum of PWB, SFWB, EWB, FWB and BCS subscale scores (37 items)

NOTE: All items were scored so that a higher score indicated a higher QoL measure. Prorating a subscale score was acceptable if 50% or more items in a particular subscale were answered. Abbreviations: TOI, FACT-B Trial Index; FACT-G, Functional Assessment of Cancer Therapy-General.

[a] Indicated negatively written items and were scored as followed: 0, very much; 1, quite a bit; 2, somewhat; 3, a little bit; and 4, not at all.

[b] Indicated positively written items and were scored as followed: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much.

[c] FACT-G and FACT-B scores were calculated if overall item response rate was 80% or higher.

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CONCLUSION

Summary

The major objectives of this doctoral dissertation project were to first define and quantify AL load, as a measure of cumulative stress, and then to identify predictors and consequences of higher AL among Black WCHFS participants with non-metastatic BrCa, who have relevant data available obtained from baseline and F/U interviews, and agreed to all medical records release. The objectives were accomplished by addressing the specific aims. For specific Aim 1, AL scores were computed using two methods, and important risk factors of AL calculated by both computation methods were determined in Chapter 1. The consequences of higher AL, namely tumor clinicopathological features and QoL were the major keys being addressed in specific Aim 2, and they are discussed separately in Chapters 2 and 3.

In Chapter 1, we have demonstrated that AL scores determined by lipid-profile based biomarkers and inflammatory-index based biomarkers have moderate-to-fair agreement (kappa=0.504), suggesting that albumin, eGFR and BMI can be utilized as alternative substitutes for lipid biomarkers for AL computation, given that lipid profiles are not ordered as commonly as routine CMP. The concordance of AL measure 1 and AL measure 2 was also supported by our sensitivity analysis, which only focused on 229 women who had data available on lipid-profile based biomarkers and inflammatory-index based biomarkers. AL measure 1 and AL measure 2 did not demonstrate good-to-excellent agreement, and therefore may not always be used interchangeably.

This observation is as expected because lipid disorders, which are normally correlated with obesity, may not be directly related to abnormal albumin and eGFR results (e.g., inflammation and organ failure). The relationship between lower SES and higher AL was comparable to previous studies, however, this study failed to find significant associations between neighborhood perceptions, unhealthy lifestyles and behaviors, food and nutrients intake, and AL, irrespective of the computation method used. Given that this study was limited by a relatively small sample size, larger longitudinal studies could be undertaken to further investigate the predictors of cumulative stress among Black BrCa survivors, and clarify our research findings.

The main focus of Specific Aim 2 was to examine the potential consequences of high cumulative stress, using AL computed by the two methods in Chapter 1. The major highlight from Chapter 2 was that this is the first study, to our knowledge, to evaluate the consequences of AL with respect to breast tumor phenotypes in Black BrCa survivors. Higher AL was found to be a significant risk factor for aggressive tumor characteristics, namely higher tumor grade and larger tumor size. As expected, more significant findings were reported when using AL measure 2 due to a higher statistical power. Findings from this Chapter potentially illustrated some sociobiologic explanations for the observations that Black women are more likely to be diagnosed with aggressive tumor characteristics compared to women in other ethnic groups. Future research to clarify the relationship between AL and breast tumor biology is therefore warranted.

Lastly, Chapter 3 focused on QoL measures among Black BrCa survivors using FACT-B data reported one year after BrCa diagnosis. We hypothesized that poorer QoL was one of the potential consequences of higher AL among Black BrCa survivors. Findings from this Chapter suggested that QoL measured by physical well-being (PWB), functional well-being (FWB) and general FACT-G scores were potential consequences of AL. Although no other FACT-B subscales and derived total scores were shown to be significant consequences of AL, these null findings might be largely attributed to a relatively small sample size, and the use of a dichotomized version of FACT-B scores resulting from highly skewed FACT-B data in WCHFS. Nevertheless, the significant relationship observed between higher AL and poorer PWB, FWB, and FACT-G, might have utility in elucidating the potential causes of overall lower QoL in Black BrCa survivors, and hence could inform the development and implementation of targeted interventional strategies to improve QoL in Black BrCa survivors. Further longitudinal studies using additional QoL measures are warranted to investigate the associations of AL with QoL among Black BrCa survivors.

Public Health Implications

To date, limited studies have examined the factors that are associated with cumulative stress and the potential consequences of cumulative stress among Black women with BrCa. Findings from this study, therefore, addressed several important gaps in the literature and contributes to advancing the current stage of knowledge in the field of BrCa epidemiology. And more importantly, this study

may provide some additional insight into the sociobiologic contributors to poorer BrCa outcomes among Black women. Higher cumulative stress has historically disproportionally affected Black women, thus, investigations on the causes and consequences of cumulative stress will be particularly useful in elucidating strategies for improving BrCa outcomes in Black women and addressing racial/ethnic disparities in BrCa outcomes.

From a public health perspective, understanding how cumulative stress impacts BrCa outcomes in Black women is of critical relevance, so that healthcare practitioners can develop better interventional strategies to help Black BrCa survivors stay healthy with optimized outcomes. For instance, public health practitioners in the State of New Jersey, for instance, might consider offering free health promotion classes in major communities where most Black women reside (e.g., Newark, Camden), and educate women how to maintain a healthy weight by modifying lifestyle and behaviors in order to reduce cumulative physiological stress. Black BrCa survivors are also encouraged to work closely with their primary care physicians (PCPs), who are responsible for the coordinated care and comorbidity management. As healthcare providers, PCPs should play the key role in managing chronic diseases, especially obesity, diabetes, hypertension, and dyslipidemia in Black women, so that cumulative physiological stress can be effectively controlled at a lower level. Cancer specialists (e.g., oncologists, radiologists, surgeons) should also be aware when their patients have comorbidities for which treatments may impact BrCa progression and outcome, so that they can work with collaboratively with PCPs and other

providers (e.g., cardiologists, endocrinologists) to achieve the best possible health outcomes among Black BrCa survivors.