

Prediagnostic Allostatic Load as a Predictor of Poorly Differentiated and Larger Sized Breast Cancers among Black Women in the Women's Circle of Health Follow-Up Study



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ABSTRACT

Background: Few studies have empirically tested the association of allostatic load (AL) with breast cancer clinicopathology. The aim of this study was to examine the association of AL, measured using relevant biomarkers recorded in medical records before breast cancer diagnosis, with unfavorable tumor clinicopathologic features among Black women.

Methods: In a sample of 409 Black women with nonmetastatic breast cancer who are enrolled in the Women's Circle of Health Follow-Up Study, we estimated prediagnostic AL using two measures: AL measure 1 [lipid profile–based—assessed by systolic and diastolic blood pressure (SBP, DBP), high-density lipoprotein, low-density lipoprotein, total cholesterol, triglycerides, and glucose levels; waist circumference; and use of diabetes, hypertension, or hypercholesterolemia medication] and AL measure 2 (inflammatory index–based—assessed by SBP, DBP, glucose, and albumin

levels; estimated glomerular filtration rate; body mass index; waist circumference; and use of medications previously described). We used Cohen's statistic to assess agreement between the two AL measures and multivariable logistic models to assess the associations of interest.

Results: AL measures 1 and 2 moderately agreed ($\kappa = 0.504$). Higher prediagnostic AL predicted higher grade (poorly differentiated vs. well/moderately differentiated) using AL measure 1 [OR = 2.16; 95% confidence interval (CI), 1.18–3.94] and AL measure 2 (OR = 1.60; 95% CI, 1.02–2.51), and larger tumor size (≥ 2 cm vs. < 2 cm; OR = 1.58; 95% CI, 1.01–2.46) using AL measure 2 only.

Conclusions: Elevated prediagnostic AL might contribute to more unfavorable breast cancer clinicopathology.

Impact: Addressing elevated prediagnostic levels of AL has potentially important clinical implications.

Introduction

Increased breast cancer mortality among African American/Black women (referred to hereafter as Black) can be partially attributed to earlier age at diagnosis and differences in breast cancer clinicopathologic features, which plausibly contribute to increased mortality rates in this group (1–3). It is clear that the reasons for breast cancer mortality inequities are complex (4, 5), and might result from combined effects of intrinsic biological factors (e.g., hormone receptor status, genetic alterations, molecular subtypes) as well as nonbiological factors (e.g., social determinants of health). In terms of the potential

impacts of nonbiological factors that might contribute to aggressive breast cancer phenotypes and poorer outcomes, Black women tend to experience higher levels of health-adverse psychosocial stressors (e.g., discrimination, socioeconomic resources, social and physical disorder) than non-Hispanic White women in the United States (6–8), which might lead to adverse health outcomes (8–11), potentially including poorer breast cancer outcomes.

Such experiences likely contribute to the cumulative physiologic stress and wear and tear on the body (6, 12–16). Allostasis (or adaptive response) describes how the human body's systems release chemical messengers to promote necessary adaptive regulatory processes during exposures to external stressors (11, 17). Allostasis is a necessary component of maintaining homeostasis and health status (18). However, the process of achieving and maintaining allostasis can fail due to dysregulation of the physiologic systems involved in homeostasis. The term to describe and measure the cost of this maladaptive process is “allostatic load” (AL; refs. 18, 19). AL has been operationalized as an index that captures cumulative physiologic effects (including the body's response to chronic physiologic stress) across major regulatory systems, resulting from dysregulation of primary mediators in the hypothalamic pituitary adrenal (HPA) axis (18). This dysregulation subsequently leads to various downstream effects, including cardiovascular and metabolic outcomes that lead to increased risks of various chronic diseases (e.g., hypertension, hyperlipidemia, cardiovascular disease, etc.; ref. 20). Emerging data also implicate AL in breast cancer etiology (21). AL has been estimated using various combinations of biomarkers from the neuroendocrine, metabolic, cardiovascular, and/or the immune categories [e.g., cortisol, systolic blood pressure

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(SBP) and diastolic blood pressure (DBP), body mass index (BMI), C-reactive protein; refs. 19–27).

Although there is currently no recognized gold-standard measure used consistently to estimate AL (26, 27), it is thought that this index might serve as a suitable indicator of the cumulative health deterioration (or “weathering”; refs. 24, 28) that may contribute to increased breast cancer risk (21). Recent data from the National Health and Nutrition Examination Survey (NHANES) showed that higher AL was significantly associated with increased breast cancer risk among Black women (21); however, this association was null among White women. The concept underlying the potential role of AL on breast cancer is that the physiologic responses that are initiated and maintained in an attempt to achieve allostasis, particularly in response to exposures related to chronically stressful conditions (e.g., long-term exposure to economic, social, and/or other types of stressors), might contribute to more aggressive tumor phenotypes, and subsequently shortened survival (29–33).

In this study, we selected two different measures of prediagnostic AL. These measures were selected on the basis of computation methods used in prior literature (21–23, 25, 28), as well as on data quality and availability of relevant biomarkers in our study sample, to assess associations of prediagnostic AL with breast cancer clinicopathology among Black women. Further, given the associations of obesity, related comorbid conditions, and inflammation with breast cancer (34), the two AL measures explored in this study might prove to be important biomarkers for understanding breast cancer risk and outcomes, particularly among Black women. Evidence from the literature support the concept that these AL measures could reliably capture lipid/metabolic pathways (AL measure 1) and the inflammatory pathway (AL measure 2; refs. 22, 23, 25, 27, 28), and that such measures of chronic physiologic stress potentially influence breast cancer risk and outcomes (21, 34, 35). We specifically sought to explore the association of prediagnostic AL measures with several unfavorable tumor clinicopathologic features, namely invasive tumor behavior, higher tumor grade, larger tumor size, and estrogen receptor negative (ER⁻) status in the Women’s Circle of Health Follow-Up Study (WCHFS). We hypothesized that elevated pre-diagnostic AL is associated with the more aggressive breast cancer clinicopathologic features that are frequently diagnosed among Black women, which is linked to the increased breast cancer mortality risk in this group.

Materials and Methods

Study sample and data collection

The WCHFS (36) collected longitudinal data among a large, population-based cohort study of Black breast cancer survivors identified and recruited in 10 counties in New Jersey. The WCHFS was established to evaluate the prognostic role of obesity, obesity-related comorbidities, and related biologic pathways on survival and quality of life among Black breast cancer survivors. Incident, primary breast cancer cases were identified through rapid case ascertainment by the New Jersey State Cancer Registry in 10 counties in New Jersey. Breast cancer cases with histologically confirmed ductal carcinoma *in situ* (DCIS) or invasive breast cancer, who self-identified as African American/Black, ages 20 to 75 years, able to complete an interview in English, and had no history of cancer, were eligible to participate. This study was approved by the Institutional Review Boards of all participating institutions and all study participants provided written informed consent prior to the baseline interview.

Data used in the analysis were collected from interviews and medical records. The in-person, interviewer-administered questionnaires were

conducted at approximately 9 months after breast cancer diagnosis, and included sociodemographics, reproductive and clinical characteristics, comorbidities, and other measures. During the baseline interviews, trained research staff also collected anthropometric measurements, and body composition measures using standardized protocols (37). Medical records were obtained from providers and hospitals where breast cancer care and care for comorbid conditions were received, for two time points: (i) up to 12 months before breast cancer diagnosis; and (2) 9 to 12 months after breast cancer diagnosis. Clinical data relevant to the estimation of the primary exposure, AL, were abstracted from the time period of up to 12 months before breast cancer diagnosis. As of the start of the analysis described herein (August 15, 2018), 409 WCHFS participants had the relevant data abstracted from their medical records and available for analysis.

Variables

Dependent variables

Information on tumor characteristics was available from medical and pathology records, and “unfavorable or aggressive” tumor characteristics were defined on the basis of four clinicopathologic features: (i) tumor behavior [invasive (stages I, II, and III) vs. noninvasive (stage 0 or DCIS)]; (ii) tumor grade [poorly differentiated (grade 3) vs. well and moderately differentiated (grades 1 and 2)]; (iii) tumor size (≥ 2 cm vs. < 2 cm); and (iv) ER status (ER⁻ vs. ER⁺).

Independent variables

AL was the exposure of interest and was estimated using two computation methods. The computation methods for estimating AL were selected on the basis of previous studies (21–25) as well as on data quality and availability from medical records of relevant biomarkers collected 12 months before breast cancer diagnosis. These biomarker data were abstracted from the medical records of each participant for the period up to 12 months before breast cancer diagnosis, with the exception of waist circumference, which was measured during in-person interview within 9 months postdiagnosis. AL measure 1 was classified as a lipid profile-based measure and AL measure 2 was classified as an inflammatory profile-based measure. Although there are multiple computation methods to choose from for estimating AL (19, 21–23, 25–27, 33), in this study, eight biomarkers were available in the WCHFS database and therefore selected as contributors to the estimation of the two AL measures. SBP, DBP, waist circumference, glucose level, high-density lipoprotein (HDL) level, and total cholesterol [with consideration of low-density lipoprotein level (LDL) level if total cholesterol ≤ 240 mg/dL], triglyceride level, and use of medications to control hypertension, diabetes, or hypercholesterolemia were included in the computation of AL measure 1 (21, 22, 24). SBP, DBP, waist circumference, glucose level, use of medications to control hypertension, diabetes, or hypercholesterolemia, albumin level, estimated glomerular filtration rate (eGFR), and BMI were included in the computation of AL measure 2 (21–25).

Previous studies have computed AL using summed risk indices for each biomarker included in the computation method (to first obtain a summed, continuous score which was then dichotomized using a cutoff value; refs. 19, 21, 22, 24, 26, 27). We similarly used a cutoff value to assign each biomarker a threshold of risk that determined the score (0 or 1) that each biomarker would contribute to the computed AL score. The following cutoff values were used to indicate high-risk (score of 1 point to the AL computation): (i) SBP ≥ 140 mmHg; (ii) DBP ≥ 90 mmHg; (iii) waist circumference ≥ 88 cm; (iv) glucose level ≥ 110 mg/dL; (v) HDL < 50 mg/dL; (vi) total cholesterol > 240 mg/dL or total cholesterol ≤ 240 mg/dL and LDL > 130 mg/dL; (vii) triglycerides

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≥150 mg/dL; (viii) ever use of medications to control hypertension, diabetes, or hypercholesterolemia; (ix) eGFR <59 mL/min; (x) albumin <4 g/dL; and (xi) BMI ≥30 kg/m². Ultimately, points were summed to obtain continuous measure for AL measures 1 and 2, each with maximum possible score of 8 (range: 0–8). These measures were then dichotomized using the median of each measure as the cutoff (median = 3 points; lower AL, 0–3 points; higher AL, 4–8 points; refs. 19, 21, 22, 24, 26, 27). Cohen's Kappa statistic (κ) was calculated to test the agreement between AL measures 1 and 2.

Statistical analysis

Descriptive statistics (frequencies and proportions) were calculated to describe the sociodemographic, reproductive characteristics and medical history, and tumor clinicopathologic characteristics of the study sample separately by AL measure cohort (AL measure 1 cohort, $n = 229$; AL measure 2 cohort, $n = 409$). The sample size of these groups differed due to data availability of the component biomarkers of each AL measure. Prior to analyzing the associations of interest, κ statistics were used to test the agreement between AL measure 1 and AL measure 2 for the 229 participants with data available for both AL measures. We estimated ORs and 95% confidence intervals (CI), using separate unadjusted and adjusted logistic regression models, to describe the associations of higher AL measure 1 and higher AL measure 2 with tumor behavior, tumor grade, tumor size, and ER status. Adjusted models controlled for age at diagnosis (continuous), birthplace (US-born, foreign-born), marital status (married/living as married, separated/divorced/widowed, single/never married), menopausal status (premenopausal, postmenopausal), and family history of breast cancer (yes, no). Given inherent differences between noninvasive and invasive breast tumors, sensitivity analysis was performed to examine the associations of interest among women with invasive tumors only, to address the concern regarding inclusion of DCIS cases in the analysis and the potential impact of this on the observed risk estimates. Sensitivity analysis was also performed to examine the associations of AL measure 2 with the unfavorable tumor features of interest among the 229 participants with data available for both AL measures. The results were compared with the associations observed between AL measure 1 and all predictors in the same cohort. All reported P values were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed using SAS v9.4 (SAS Institute).

Results

The distribution of select characteristics among the study sample are shown in **Table 1**. Except for age at diagnosis, sociodemographics, reproductive, and clinical characteristics were similar for women in each of the AL measure cohorts. In the overall study sample, less than 20% was foreign-born. About one-third was 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. Approximately two-thirds had private or employer-sponsored insurance, while approximately 15% was enrolled in Medicaid. Nearly 60% was classified as obese (BMI ≥30.0 kg/m²). More than three-quarters was postmenopausal and a little over 25% was <12 years at menarche. Almost half reported having a family history of breast cancer, more than three-quarters reported a history of oral contraceptive, whereas less than 20% reported having a history of hormone therapy use, and more than half of parous women had a history of breastfeeding. In addition, approximately 80% women had at least one comorbid condition. In terms of breast tumor clinicopathology, among the overall study sample, approximately 45% was diagnosed with stage

Table 1. Select characteristics of the study sample of Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (2014–2018), by AL measure cohort.

	AL measure 1 cohort ($n = 229$) n (%)	AL measure 2 cohort ($n = 409$) n (%)
Sociodemographics		
Age at diagnosis (years), mean ± SD	56.6 ± 9.2	55.0 ± 10.4
Age at diagnosis (years)		
20–49	59 (25.8)	129 (31.5)
50–59	74 (32.3)	131 (32.0)
60–75	96 (41.9)	149 (36.4)
Birthplace		
U.S. born	195 (85.2)	344 (84.1)
Foreign born	34 (14.8)	65 (15.9)
Marital status		
Married or living as married	82 (35.8)	142 (34.7)
Separated/divorced/widowed	83 (36.2)	139 (34.0)
Single/never married	64 (28.0)	128 (31.3)
Education		
Below college	84 (36.7)	142 (34.7)
Technical school/some college	78 (34.1)	140 (34.2)
College graduate and above	67 (29.3)	127 (31.1)
Annual household income		
<\$20,000	59 (26.5)	98 (24.7)
\$20,000–69,999	91 (40.8)	173 (43.6)
≥\$70,000	73 (32.7)	126 (31.7)
Primary health insurance		
Medicaid	35 (15.3)	55 (13.4)
Medicare	55 (24.0)	82 (20.0)
Private/employer sponsored	128 (55.9)	246 (60.2)
Other	11 (4.8)	26 (6.4)
Reproductive characteristics and medical history		
BMI (kg/m ²), mean ± SD	32.71 ± 7.05	32.05 ± 7.03
BMI (kg/m ²)		
<25.0	23 (10.0)	54 (13.2)
25.0–29.99	73 (31.9)	127 (31.0)
30.0–34.99	51 (22.3)	98 (24.0)
≥35.0	82 (35.8)	130 (31.8)
Menopausal status		
Premenopausal	51 (22.3)	120 (29.3)
Postmenopausal	178 (77.7)	289 (70.7)
Age at menarche (years)		
<12	62 (27.2)	115 (28.2)
12–13	107 (46.9)	189 (46.3)
>13	59 (25.9)	104 (25.5)
Family history of breast cancer		
Yes	100 (43.7)	190 (46.4)
No	129 (56.3)	219 (53.6)
History of oral contraceptive use		
Yes	173 (75.6)	309 (75.6)
No	56 (24.4)	100 (24.4)
History of hormone therapy use		
Yes	39 (17.2)	65 (16.0)
No	188 (82.8)	341 (84.0)
Parity		
Nulliparous	29 (12.7)	75 (18.3)
1–2	114 (49.8)	204 (49.9)
≥3	86 (37.5)	130 (31.8)
History of breastfeeding ^a		
Yes	107 (53.5)	181 (54.2)
No	93 (46.5)	153 (45.8)

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Table 1. Select characteristics of the study sample of Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (2014–2018), by AL measure cohort. (Cont'd)

	AL measure 1 cohort (<i>n</i> = 229) <i>n</i> (%)	AL measure 2 cohort (<i>n</i> = 409) <i>n</i> (%)
Comorbid conditions		
0	36 (15.7)	91 (22.2)
1	68 (29.7)	122 (29.8)
≥2	125 (54.6)	196 (47.9)
Breast tumor clinicopathology characteristics		
Tumor stage		
Stage 0	48 (21.0)	86 (21.0)
Stage I	80 (34.9)	140 (34.2)
Stage II	86 (37.6)	145 (35.4)
Stage III	15 (6.5)	38 (9.3)
Tumor grade		
Well differentiated	33 (15.4)	55 (14.4)
Moderately differentiated	77 (36.0)	137 (35.8)
Poorly differentiated	104 (48.6)	191 (49.9)
ER status		
ER ⁺	173 (76.2)	314 (77.2)
ER ⁻	54 (23.8)	93 (22.8)
Tumor size		
<2 cm	151 (65.9)	262 (64.1)
≥2 cm	78 (34.1)	147 (35.9)

Note: Percentages may not sum to 100 due to rounding. All stage 0 cases were classified as tumor size <2 cm.

^aHistory of breastfeeding was assessed among parous women only.

II or III breast cancer, and almost half had poorly differentiated tumors. In addition, about 24% had ER⁻ disease, and more than one third was diagnosed with tumors ≥2 cm.

Table 2 depicts distributions of the various biomarkers contributing to prediagnostic AL measure 1 and AL measure 2. The computed score of AL measure 1 and AL measure 2 both ranged from 0 to 7, suggesting that there were no women who fell into the high-risk category for all eight biomarkers used in the computation of each AL measure. With respect to individual biomarkers that were originally reported as continuous variables, women in the AL measure 1 cohort had higher mean values of SBP, DBP, waist circumference, and glucose level relative to women in the AL measure 2 cohort. 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 SDs of 4.41 ± 3.92 g/dL for serum albumin level, and 32.05 ± 7.03 kg/m² for BMI. Although some lab studies reported eGFR as a continuous variable, most reports only indicated that eGFR >60 mL/min (or ≥59 mL/min) was considered as a normal test and therefore eGFR <59 mL/min was indicative of high-risk (and this variable was dichotomized in the estimation of AL measure 2).

When each of the biomarkers that contributed to prediagnostic AL measures were dichotomized, there was a higher proportion of women in the AL measure 1 cohort (65%) with lower AL score relative to those in the AL measure 2 cohort (55.50%). Further, women in the AL measure 1 cohort also had slightly higher proportions of hypertension and larger waist circumference compared with women in the AL

measure 2 cohort, whereas glucose levels were similar. More than 80% of women in each AL measure cohort had a waist circumference ≥88 cm and the proportions using medications to control diabetes, hypertension, or hypercholesterolemia in the AL measure 1 and AL measure 2 cohorts were approximately 77% and 70%, respectively. Despite some of these potential differences, concordance between the dichotomized AL measure 1 and AL measure 2 was found to be moderate-to-fair ($\kappa = 0.504$).

Associations between prediagnostic AL and the aggressive tumor characteristics of interest are shown in **Table 3**. Unadjusted associations demonstrated that higher prediagnostic AL measure 1 (score of 4–8 vs. 0–3) was associated with 87% increased odds of poorly differentiated tumors (**Table 3**). This increased risk association was consistent in the multivariable model, which controlled for age at diagnosis, birthplace, menopausal status, marital status, and family history of breast cancer (**Table 3**). In terms of AL measure 2, in the multivariable models, higher prediagnostic AL was associated with 60% increased odds of poorly differentiated tumors (OR = 1.60; 95% CI, 1.02–2.51) and 58% increased odds of tumor size ≥2 cm (OR = 1.58; 95% CI, 1.01–2.46). In sensitivity analysis, we reexamined these associations and focused on women with invasive tumors only (**Table 4**). We found a stronger risk of poorly differentiated tumors associated with higher AL measure 1 (OR = 2.49; 95% CI, 1.28–4.85) when we excluded DCIS cases. A similar magnitude of risk was observed between higher AL measure 2 and poorly differentiated tumors (OR = 1.66; 95% CI, 1.02–2.72) when DCIS cases were excluded. Likewise, although not statistically significant, with the exclusion of DCIS cases, we observed a suggestion of increased odds of ER⁻ disease associated with higher AL (OR = 1.52; 95% CI, 0.89–2.57). We also conducted sensitivity analysis to assess the association of AL measure 2 with unfavorable tumor clinicopathologic features among study participants in the AL measure 1 cohort (*n* = 229—these participants had AL computed using both AL measure 1 and AL measure 2, **Table 5**). Results were compared qualitatively with the AL measure 1 associations found in **Table 3**. A similar, two-fold increase in odds of poorly differentiated tumor associated with AL measure 2 was reported (OR = 2.10; 95% CI, 1.16–3.81) as reported for AL measure 1 (OR = 2.16; 95% CI, 1.18–3.94, **Table 3**). In addition, no other significant associations of other aggressive tumor features and AL measure 2 were observed, which were all consistent with results reported in **Table 3**.

Discussion

Emerging evidence has led to the supposition that higher AL possibly contributes to increased risks of mortality among Black women (21, 38–40), which is likely due to more aggressive phenotypes in this group (1–3). However, to our knowledge, no other study has examined the association of prediagnostic AL with breast tumor clinicopathology among Black women. In this study, we found that higher prediagnostic AL was associated with increased odds of poorer tumor differentiation and larger tumor size. There was also suggestion that higher prediagnostic AL was associated with increased odds of ER⁻ disease among invasive breast cancer cases only, although this finding did not reach statistical significance. Of note, prediagnostic AL based on the lipid profile–based measure was associated with more than two-fold increased odds of poorly differentiated versus well or moderately differentiated breast tumors and not significantly associated with any other clinicopathologic feature. Conversely, higher prediagnostic AL based on the inflammatory profile–based measure was associated with 60% increased odds of poorly differentiated versus

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Table 2. Distribution of biomarkers contributing to AL scores among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (2014–2018), by AL measure cohort.

	AL measure 1 ^a cohort (n = 229)	AL measure 2 ^b cohort (n = 409)
Biomarkers	Mean ± SD	Mean ± SD
AL score	3.09 ± 1.46	3.15 ± 1.61
SBP (mm Hg)	133.47 ± 16.53	130.74 ± 17.14
DBP (mm Hg)	79.70 ± 9.54	78.57 ± 10.18
HDL (mg/dL)	61.42 ± 17.85	
LDL (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 (%)
AL ^c		
Low (0–3 points)	149 (65.1)	227 (55.5)
High (4–8 points)	80 (34.9)	182 (44.5)
SBP ≥140 mm Hg		
Yes	79 (34.5)	120 (29.3)
No	150 (65.5)	289 (70.7)
DBP ≥90 mm Hg		
Yes	40 (17.5)	64 (15.6)
No	189 (82.5)	345 (84.4)
HDL <50 mg/dL		
Yes	66 (28.8)	
No	163 (71.2)	
LDL ≥130 mg/dL		
Yes	66 (28.8)	
No	163 (71.2)	
Total cholesterol ≥240 mg/dL		
Yes	29 (12.7)	
No	200 (87.3)	
Abnormal total cholesterol or LDL level ^d		
Yes	67 (29.3)	
No	162 (70.7)	
Triglycerides ≥150 mg/dL		
Yes	29 (12.7)	
No	200 (87.3)	
Glucose level ≥110 mg/dL		
Yes	55 (24.0)	106 (25.9)
No	174 (76.0)	303 (74.1)
Waist circumference ≥88 cm		
Yes	194 (84.7)	338 (82.6)
No	35 (15.3)	71 (17.4)
History of use of medications to control diabetes, hypertension, or hypercholesterolemia		
Yes	177 (77.3)	285 (69.7)
No	52 (22.7)	124 (30.3)
Albumin <4.0 g/dL		
Yes		111 (27.1)
No		298 (72.9)
eGFR <59 mL/min		
Yes		38 (9.3)
No		371 (90.7)

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Table 2. Distribution of biomarkers contributing to AL scores among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (2014–2018), by AL measure cohort. (Cont'd)

	AL measure 1 ^a cohort (n = 229)	AL measure 2 ^b cohort (n = 409)
BMI ≥30 kg/m ²		
Yes		228 (55.8)
No		181 (44.2)

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

^aAL measure 1 was computed on the basis of the following biomarkers: SBP, DBP, waist circumference, glucose level, HDL, triglycerides, total cholesterol and/or LDL, and use of medication to control hypertension, hypercholesterolemia, or diabetes.^bAL measure 2 was computed on the basis of the following biomarkers: SBP, DBP, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.^cThe median AL score (for both measures) among Women's Circle of Health Follow-Up Study participants was 3. Thus, 3 was used as the cutoff point to dichotomize the AL variables.^dAbnormal total cholesterol or LDL level was defined as (i) total cholesterol >240 mg/dL or (ii) total cholesterol ≤240 mg/dL and LDL >130 mg/dL.

well or moderately differentiated breast tumors and with 59% increased odds of larger tumor size (≥2 cm vs. <2 cm). These findings are interesting given the likelihood that individual biological pathways through which AL is expressed may differ by race/ethnicity as shown in analysis of NHANES data, which focused on assessing potential effect modification by race/ethnicity (27). The observation that among Blacks, AL tended to be associated with inflammatory processes, whereas among Whites, AL tended to be affected primarily through metabolic pathways might support the findings we report herein.

We used a combination of laboratory results recorded in study participant's medical records [gathered from a lipid panel (e.g., HDL, LDL, total cholesterol, and triglycerides)] along with inflammatory-based biomarkers (e.g., serum albumin), anthropometric measurements (e.g., waist circumference), and renal function (e.g., eGFR) to estimate AL scores. Overall, AL measures wear and tear on the body as a result of physiologic responses assessed from various systems, thereby providing a relatively comprehensive measure. Nearly all studies of AL (19, 21, 22, 24, 26, 27) have included at least one lipid result (HDL, LDL, total cholesterol, and/or triglycerides) for AL score computation, and several studies have also considered adding albumin and eGFR to better quantify AL (22, 41). 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 available lipid panel results, showing abnormal lipid biomarkers in their medical records were likely to be obese, and/or have metabolic syndrome-related comorbidities. According to the recommended screening guidelines (see <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/lipid-disorders-in-adults-cholesterol-dyslipidemia-screening>), women without metabolic conditions may not have their lipids measured as part of routine medical care, whereas women with a metabolic condition might have more frequent visits with a medical provider, thereby increasing the likelihood that lipid levels are available in their medical records. In contrast, albumin and eGFR results were abstracted from laboratory reports from routine comprehensive metabolic panels. Having results for this panel of tests are

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Table 3. Unadjusted and multivariable-adjusted^a logistic regression analyses of the associations between higher AL^b and unfavorable breast cancer clinicopathologic characteristics among Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (2014–2018), by AL measure cohort.

	AL measure 1 ^c cohort (n = 229)		AL measure 2 ^d cohort (n = 409)	
	Unadjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)	Unadjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)
Tumor behavior: invasive (stage I, II, and III) vs. noninvasive (stage 0 or DCIS)				
AL				
Lower (0–3)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Higher (4–8)	1.09 (0.56–2.14) P = 0.79	1.23 (0.62–2.47) P = 0.56	1.02 (0.63–1.64) P = 0.95	1.20 (0.72–1.99) P = 0.49
Tumor grade: poorly differentiated vs. well and moderately differentiated				
AL				
Lower (0–3)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Higher (4–8)	1.87 (1.06–3.30) P = 0.03	2.16 (1.18–3.94) P = 0.01	1.15 (0.77–1.71) P = 0.51	1.60 (1.02–2.51) P = 0.04
Tumor size: ≥2 cm vs. <2 cm				
AL				
Lower (0–3)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Higher (4–8)	0.90 (0.51–1.60) P = 0.72	1.00 (0.55–1.84) P = 0.99	1.22 (0.81–1.83) P = 0.34	1.58 (1.01–2.46) P = 0.04
ER status: ER ⁻ vs. ER ⁺				
AL				
Lower (0–3)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Higher (4–8)	1.17 (0.62–2.20) P = 0.64	1.12 (0.59–2.16) P = 0.73	1.24 (0.78–1.98) P = 0.36	1.23 (0.75–2.01) P = 0.41

Note: All stage 0 cases were classified as tumor size <2 cm. Bold values indicate statistical significance.

^aThe following covariates were included in the multivariable-adjusted regression analyses: (i) age at diagnosis; (ii) birthplace; (iii) marital status; (iv) menopausal status; (v) family history of breast cancer.

^bThe median AL score among Women's Circle of Health Follow-Up Study participants was 3. Thus, 3 was used as the cutoff point to dichotomize the allostatic load variable.

^cAL measure 1 was computed on the basis of the following biomarkers: SBP, DBP, waist circumference, glucose level, HDL, triglycerides, total cholesterol and/or LDL, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

^dAL measure 2 was computed on the basis of the following biomarkers: SBP, DBP, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.

not always associated with being obese or having metabolic syndrome in general. As such, albumin and eGFR could provide additional important biomarkers for AL computation that are unrelated to a patient having obesity-related comorbid conditions.

Thus, in this study, the inclusion of albumin and eGFR results along with BMI allowed us to estimate AL using a second measure (the inflammatory profile-based measure). This allowed us to include more women who had fewer comorbid conditions and to assess agreement of this measure with the lipid profile-based measure. The resulting Cohen's κ coefficient ($\kappa = 0.504$) was indicative of moderate agreement. The fair concordance between AL measure 1 and AL measure 2 was further supported by our sensitivity analysis, given that similar associations for AL measure 1 and AL measure 2 scores with unfavorable tumor clinicopathologic features were observed among the 229 study participants for whom biomarkers were available for computing both AL measure 1 and AL measure 2 (Table 5). This result was expected because lipid disorders are not directly related to hypoalbuminemia (e.g., low serum albumin) or kidney failure (e.g., low eGFR). Further, given the association of inflammatory markers with obesity, AL measure 2 might also be expected to be associated with dyslipidemia (42). Although the differences in mean score between AL measure 1 and AL measure 2 were minimal, a lower proportion of women in the AL measure 1 cohort (34.9%) was classified as having higher AL, relative to those in the AL measure 2 cohort (44.5%). A strong correlation between abnormal lipid profiles and obesity, as well

as the observation of a higher obesity prevalence among Black women, would possibly explain such differences.

Coexistence of metabolic syndrome-related chronic diseases (e.g., hypertension, diabetes, cardiovascular disease) is common among Black women with breast cancer and can have detrimental impacts on breast cancer progression and survivorship (43–48). It has been widely accepted that aggressive tumor characteristics, which are the potential consequences of metabolic syndrome-related chronic diseases, can also have a substantive negative impact on breast cancer survivorship. However, the biological mechanisms underlying the causes of aggressive breast tumor clinicopathologic features that are ultimately associated with increased mortality among Black women remain unclear. To date, only one published study has discussed the impact of AL on health outcomes in Black women at the cellular level, suggesting that epigenetic changes, namely DNA methylation, alterations on covalent histone modifications, aberrant changes in expression of miRNA and long noncoding RNA, play important roles (49). As expected, our study showed that higher prediagnostic AL was significantly associated with higher tumor grade and larger tumor size among Black breast cancer survivors. This is important given that tumor grade and tumor size are 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. The latter result might be attributed to smaller numbers of stage

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Table 4. Multivariable-adjusted^a logistic regression analyses of the associations between higher AL^b and unfavorable breast cancer clinicopathologic characteristics among Black invasive breast cancer survivors in the Women's Circle of Health Follow-Up Study (2014–2018), by AL measure cohort.

	AL measure 1 ^{c,d} cohort (n = 181) Multivariable-adjusted OR (95% CI)	AL measure 2 ^{e,f} cohort (n = 323) Multivariable-adjusted OR (95% CI)
Tumor grade: poorly differentiated vs. well and moderately differentiated		
AL		
Lower (0–3)	1.00 (referent)	1.00 (referent)
Higher (4–8)	2.49 (1.28–4.85) P = 0.007	1.66 (1.02–2.72) P = 0.04
Tumor size: ≥2 cm vs. <2 cm		
AL		
Lower (0–3)	1.00 (referent)	1.00 (referent)
Higher (4–8)	0.93 (0.49–1.79) P = 0.38	0.93 (0.49–1.79) P = 0.38
ER status: ER ⁻ vs. ER ⁺		
AL		
Lower (0–3)	1.00 (referent)	1.00 (referent)
Higher (4–8)	1.27 (0.63–2.57) P = 0.51	1.52 (0.89–2.57) P = 0.12

Note: Bold values indicate statistical significance.

^aThe following covariates were included in the multivariable-adjusted regression analyses: (i) age at diagnosis; (ii) birthplace; (iii) marital status; (iv) menopausal status; (v) family history of breast cancer.^bThe median AL score among Women's Circle of Health Follow-Up Study participants was 3. Thus, 3 was used as the cutoff point to dichotomize the AL variable.^cAL measure 1 was computed on the basis of the following biomarkers: SBP, DBP, waist circumference, glucose level, HDL, triglycerides, total cholesterol and/or LDL, and use of medication to control hypertension, hypercholesterolemia, or diabetes.^dIncluded Women's Circle of Health Follow-Up Study participants who were diagnosed with stage I, II, and III cancer in the AL measure 1 group (n = 181).^eAL measure 2 was computed on the basis of the following biomarkers: SBP, DBP, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.^fIncluded Women's Circle of Health Follow-Up Study participants who were diagnosed with stage I, II, and III cancer in the AL measure 2 group (n = 323).

III and ER⁻ tumors among the WCHFS participants included in these preliminary analyses. We will address this concern in future analysis with a much larger sample size, and also explore the associations of interest with additional breast tumor features that are indicative of more aggressive breast cancer clinicopathology (e.g., high Ki67 proliferation marker, HER2⁺ status, triple-negative breast cancer subtype).

This study has some limitations that should be considered. We acknowledge the possibility that using alternative computation methods to estimate AL scores could yield observations and/or interpretations that differ from those reported herein. The relatively small sample size was also an obvious limitation. The inclusion of waist circumference (which was measured within 9 months after diagnosis during the baseline study assessment) in the computation of AL measure 1 was also a potential limitation, although we do not anticipate that this concern detracts from our findings as anthropometric measurements did not change much in this period in our

Table 5. Unadjusted and multivariable-adjusted^a logistic regression analyses of the associations between higher AL^b measure 2^c and unfavorable breast cancer clinicopathologic characteristics among 229 Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (2014–2018) with both AL measures computed.

	AL measure 1 cohort ^d (n = 229)	
	Unadjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)
Tumor behavior: invasive (stage I, II, and III) vs. noninvasive (stage 0 or DCIS)		
AL		
Lower (0–3)	1.00 (referent)	1.00 (referent)
Higher (4–8)	1.01 (0.53–1.90) P = 0.99	1.23 (0.63–2.41) P = 0.55
Tumor grade: poorly differentiated vs. well and moderately differentiated		
AL		
Lower (0–3)	1.00 (referent)	1.00 (referent)
Higher (4–8)	1.63 (0.95–2.79) P = 0.08	2.10 (1.16–3.81) P = 0.01
Tumor size: ≥2 cm vs. <2 cm		
AL		
Lower (0–3)	1.00 (referent)	1.00 (referent)
Higher (4–8)	1.22 (0.71–2.11) P = 0.48	1.37 (0.76–2.46) P = 0.30
ER status: ER ⁻ vs. ER ⁺		
AL		
Lower (0–3)	1.00 (referent)	1.00 (referent)
Higher (4–8)	1.14 (0.62–2.09) P = 0.68	1.07 (0.56–2.02) P = 0.84

Note: Bold values indicate statistical significance.

^aThe following covariates were included in the multivariable-adjusted regression analyses: (i) age at diagnosis; (ii) birthplace; (iii) marital status; (iv) menopausal status; (v) family history of breast cancer.^bThe median AL score among Women's Circle of Health Follow-Up Study participants was 3. Thus, 3 was used as the cutoff point to dichotomize the AL variable.^cAL measure 2 was computed on the basis of the following biomarkers: SBP, DBP, waist circumference, glucose level, albumin, eGFR, BMI, and use of medication to control hypertension, hypercholesterolemia, or diabetes.^dAL measure 1 cohort (n = 229) included Women's Circle of Health Follow-Up Study participants with biomarkers contributing to AL measure 1 computation (SBP, DBP, waist circumference, glucose level, HDL, triglycerides, total cholesterol and/or LDL, and use of medication to control hypertension, hypercholesterolemia, or diabetes) and AL measure 2 computation as described above.

cohort. Another potential limitation is the inclusion of blood pressure measurements in the computation of AL measures given the substantial variability of blood pressure. The inclusion of study participants with both invasive and noninvasive tumors in our primary analysis could have impacted our findings given that invasive tumors are inherently more aggressive than noninvasive tumors. We addressed this concern through sensitivity analysis among invasive cases only and found that association between prediagnostic AL and higher tumor grade was consistent, with a slightly elevated magnitude of risk for AL measure 1 among invasive cases. But the association between prediagnostic AL measure 2 and larger tumor size was no longer statistically significant among invasive cases only. Likewise, although not statistically significant, excluding DCIS cases also led to higher odds of having ER⁻ disease, thus our future analysis of a larger study sample will exclude DCIS cases and reexamine the association.

Allostatic Load and Breast Cancer among Black Women

Some of the strengths of this study include the utilization of a population-based cohort of well-defined, nonmetastatic breast cancer cases diagnosed among Black women (with detailed data available through collection and abstraction of medical and pathology records as well as through interviewer-administered questionnaires) to address our research question. Also, for information available from both questionnaire data and medical records data, we prioritized data abstracted from medical records; and in cases where the preferred source was missing or questionable, the secondary data source was utilized, thereby increasing our analytical sample and minimizing information bias.

In conclusion, this study contributes to the limited available data on the consequences of higher prediagnostic AL among Black women with breast cancer, with a major focus on breast cancer clinicopathologic features. Findings from this study contribute important knowledge on factors that might be related to the development of more aggressive breast cancer phenotypes among Black women, who are at increased risk of breast cancer mortality compared with non-Hispanic White women. Additional research with a focus on the mechanisms underlying aggressive breast tumor clinicopathology, which lead to poorer outcomes among Black women are essential.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Prediagnostic Allostatic Load as a Predictor of Poorly Differentiated and Larger Sized Breast Cancers among Black Women in the Women's Circle of Health Follow-Up Study

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