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EPIDEMIOLOGY

Pre-diagnostic allostatic load and health-related quality of life in a cohort of Black breast cancer survivors

Cathleen Y. Xing[1] · Michelle Doose[1,2] · Bo Qin[2,3] · Yong Lin[1,2] · Tiffany L. Carson[4] · Jesse J. Plascak[1,2] · Kitaw Demissie[5] · Chi-Chen Hong[6] · Elisa V. Bandera[1,2,3] · Adana A. M. Llanos[1,2]

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Abstract

Purpose To determine the association of pre-diagnostic allostatic load (AL) with health-related quality of life (HRQOL) among Black women with breast cancer.

Methods In a sample of 409 Black women with non-metastatic breast cancer enrolled in the Women's Circle of Health Follow-Up Study (WCHFS), two pre-diagnostic AL measures were estimated using medical records data from up to 12 months prior to breast cancer diagnosis: AL-lipid/metabolic profile-based measure and AL-inflammatory profile-based measure. HRQOL was assessed approximately 24 months post diagnosis, using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) instrument, including 5 subscale scores [presented by physical well-being (PWB), social & family well-being (SFWB), emotional well-being (EWB), functional well-being (FWB), and breast cancer-specific scale (BCS)] and 3 derived total scores [presented by trial outcome index (TOI), Functional Assessment of Cancer Therapy-General (FACT-G) and FACT-B]. We used multivariable logistic regression models, using dichotomized AL scores (lower AL: 0–3 points, higher AL: 4–8 points), to assess the associations between the two pre-diagnostic AL measures and HRQOL.

Results Higher pre-diagnostic AL was associated with poorer FWB and lower FACT-G, but these associations were statistically significant for the AL-inflammatory profile-based measure (FWB: OR 1.63, 95% CI 1.04, 2.56; FACT-G: OR 1.62, 95% CI 1.04, 2.54), but not the AL-lipid/metabolic profile-based measure (FWB: OR 1.45, 95% CI 0.81, 2.59; FACT-G: OR 1.33, 95% CI 0.75, 2.37).

Conclusion These findings suggest that higher AL, particularly when measured using the inflammatory profile-based measure, was associated with poorer HRQOL, namely FWB and FACT-G, among Black breast cancer survivors.

Keywords Breast cancer survivorship · Health-related quality of life · Black women · Longitudinal study · Allostatic load

Background

Increased breast cancer (BC) mortality [1] and poorer health-related quality of life (HRQOL) [2] during survivorship among African American/Black women (referred to hereafter as Black) might be partially attributed to earlier age at diagnosis and more aggressive tumor clinicopathological features [1]. Black women tend to experience higher levels of health-adverse psychosocial stressors (e.g., discrimination, socioeconomic deprivation, social and physical disorder) than non-Hispanic White women in the United States (U.S.) [3], which likely contributes to higher levels of cumulative physiologic stress and wear and tear on the body [3, 4]. Allostatic load (AL) is intended to measure cumulative physiological stress across major regulatory systems (e.g., endocrine, metabolic, cardiovascular,

✉ Adana A. M. Llanos
Adana.Llanos@Rutgers.edu

1 Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA

2 Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA

3 Department of Medicine, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

4 Division of Preventive Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA

5 Department of Epidemiology and Biostatistics, SUNY Downstate Health Sciences University School of Public Health, Brooklyn, NY, USA

6 Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

immune), resulting from dysregulated stress hormones in the hypothalamic–pituitary–adrenal axis [5]. This dysregulation subsequently leads to various adverse health outcomes (e.g., inflammation, cardiovascular and metabolic outcomes, increased risks of chronic diseases including hypertension, hyperlipidemia) and affects morbidity and mortality [6]. It is thought that AL might serve as a suitable indicator of the cumulative health deterioration or "weathering" [7] that may contribute to poorer BC survival among Black women.

Mental distress is one of the most frequently reported HRQOL concerns among BC survivors [8, 9], and it is often related to the fear of cancer recurrence [10, 11], worry about other adverse health outcomes [12], and concerns about whether a family member might develop BC someday [13]. Studies have demonstrated that approximately 30–50% of BC survivors have experienced mental and psychological distress and the odds of having mental distress among BC survivors is much higher compared to the general population [14, 15]. In addition to mental and psychological distress, many BC survivors are continuously affected by other factors related to HRQOL, such as pain [16, 17], poor sexual function [16, 17], and sleep problems [16, 18–20]. Few studies to date, however, have focused on Black BC survivors and the determinants of poorer HRQOL in this group.

Two studies, utilizing NHANES data, have investigated the association of cumulative stress, measured by AL, in association with HRQOL and highlighted the need for more research in racial/ethnic minority groups [21, 22]. One study observed significantly higher levels of AL and unhealthy behaviors among Blacks and Latinos than Whites, although higher AL was not associated with risk of depressive symptoms in any group [22]. The other study [21] reported a significant positive association between AL and sleep apnea and other sleep disorders. These studies focused on non-cancer groups. To date, no study has assessed the relationship between pre-diagnostic AL and post-diagnostic HRQOL among BC survivors. Understanding this relationship among Black BC survivors is of particular interest because Black women are generally more susceptible to higher AL and lower HRQOL. Our hypothesis that higher pre-diagnostic AL is associated with poorer HRQOL among Black women diagnosed with BC was addressed using the Women's Circle of Health Follow-Up Study (WCHFS). To help operationalize composite measures of AL relevant to BC outcomes that can potentially be used in future large-scale studies, we examined two AL measures based on previously validated methods for constructing AL indices using data commonly available in medical records.

Methods

Study sample and data collection

The WCHFS is a longitudinal study of Black BC survivors in New Jersey [23, 24]. BC cases in ten New Jersey counties with histologically confirmed ductal carcinoma in situ or invasive BC, who self-identified as African American/Black, ages 20–75 years, able to speak and understand English, and with no history of cancer, were recruited through the New Jersey State Cancer Registry.

Baseline data were collected through in-person, interviewer-administered questionnaires at approximately 9 months after BC diagnosis, and pre-diagnostic information on sociodemographics, reproductive and clinical characteristics, comorbidities, and other measures were surveyed [25]. During the baseline assessment, research staff also collected anthropometric measurements, and body composition measures using standardized protocols [26]. Additional baseline data were obtained from medical records retrieved from healthcare providers where participants received their BC and comorbidity care. Clinical data relevant to the computation of pre-diagnostic AL (e.g., biomarkers from blood work), were abstracted from medical records from up to 12 months (median = 6 months) before BC diagnosis [24]. The follow-up 1 (F/U 1) assessment, administered at approximately 24 months post-diagnosis, collected survivorship data, including short-term HRQOL measures and lifestyle changes [25]. The current analysis included Black women with BC who enrolled in WCHFS from April 2014 to August 2018, consented to medical records release, and completed the baseline and F/U 1 assessments by August 2018 ($n = 409$). 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.

Measures

We estimated AL (exposure) using two computation methods: (1) AL-lipid/metabolic profile-based measure and (2) AL-inflammatory profile-based measure [24]. To compute the lipid/metabolic profile-based measure, systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, glucose level, high-density lipoprotein (HDL) level, and total cholesterol [with consideration of low-density lipoprotein (LDL) level if total cholesterol < 240 mg/dL], triglyceride level, and use of medications to control hypertension, diabetes, or hypercholesterolemia were included. To compute the inflammatory profile-based

measure, we included SBP, DBP, waist circumference, glucose level, use of medications to control hypertension, diabetes, or hypercholesterolemia, serum albumin level, estimated glomerular filtration rate (eGFR), and body mass index (BMI). Both AL measures were calculated using summed risk indices for each biomarker included in the computation. The continuous AL score was then dichotomized using the median score as the cut-off (lower AL, 0–3 points; higher AL, 4–8 points) [24].

HRQOL (outcome) data were collected during F/U 1 assessment using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) questionnaire, which is a valid and reliable measure for capturing BC-specific HRQOL [27], with a total of 37 questions grouped into 5 subscales (physical well-being (PWB), 0–28 points; social & family well-being (SFWB), 0–28 points; emotional well-being (EWB), 0–24 points; functional well-being [FWB, 0–28 points; and BC-specific scale (BCS), 0–40 points] [28], where higher scores indicated better HRQOL. In addition to the 5 subscales, trial outcome index (TOI), FACT-G, and FACT-B [28] are derived by summing specific subscale scores. All subscale scores and derived total scores were calculated as continuous variables, then dichotomized using a median cut-off [24]. Given that normality assumptions were violated (even after transformations), we performed logistic regression analysis following the approach of Kroenke et al. [29]. In sensitivity analysis to compare findings from linear regression models (with FACT-B measures modeled as continuous variables [30, 31]) to logistic regressions models (with FACT-B measures as binary variables), we found no difference in the magnitude or direction of the reported associations. Thus, findings from logistic models are reported.

Data analysis

Descriptive statistics (frequencies and proportions) were calculated to describe the sociodemographic, reproductive characteristics and medical history, tumor clinicopathology, and AL score and biomarker characteristics of the study sample separately by AL measure group. Sample size of 2 AL measure groups differed due to data availability of the component biomarkers of each AL measure. Descriptive statistics with respect to all FACT-B variables were reported separately for the $n = 409$ individuals for which calculation of the AL-inflammatory profile-based measure was possible and the $n = 229$ subset with data that allowed for calculation of the lipid/metabolic profile-based measure. To evaluate relationships between indices of AL with HRQOL measures, unadjusted logistic regression models were used to calculate odds ratios (ORs) and 95% confident intervals (CIs). Multivariable logistic regression models were used to describe the adjusted associations, where we modeled the odds of poorer HRQOL by levels of AL (high vs. low). The multivariable models controlled for age at diagnosis (continuous), birthplace (US-born, non-US-born), marital status (married/living as married, separated/divorced/widowed, single/never married), menopausal status (premenopausal, postmenopausal), family history of BC (yes, no), and number of comorbidities (none, more than one). All analyses were performed using SAS Version 9.4 (SAS institute, Inc., Cary, North Carolina).

Results

Distributions of AL measures

The distributions of select characteristics among WCHFS participants are presented in Table 1. Similar distributions of sociodemographics, reproductive characteristics and medical history were observed among women with available data on the AL-lipid/metabolic profile-based measure and women with available data on the AL-inflammatory profile-based measure, as the AL-lipid/metabolic profiled-based measure group was a subset of the AL-inflammatory profile-based measure group. Lipid biomarkers (HDL, LDL, total cholesterol, and triglycerides) were only applicable to the computation of the AL-lipid/metabolic profile-based measure. Mean values with standard deviations (SD) 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. Likewise, serum albumin level and BMI were only included in the computation of the AL-inflammatory profile-based measure and the means and SDs were 4.41 ± 3.92 g/dL for serum albumin and 32.05 ± 7.03 kg/m^2 for BMI. Although eGFR was reported as a continuous variable in some medical records, in most records, however, eGFR was reported as "normal" if eGFR was ≥ 59 ml/min (with no data included on the actual value), and therefore in the computation of the AL-inflammatory profile-based measure, eGFR < 59 ml/min was used as a cut-off to dichotomize this variable (e.g., normal eGFR = low-risk, low eGFR = high-risk).

Item-specific, subscale, and derived total HRQOL scores

The distributions of the HRQOL measures presented by item-specific, subscale and derived total scores among women in the AL-lipid/metabolic profile-based measure group are shown in Table 2. More than half of the item-specific questions listed in the PWB and SFWB subscales, and all item-specific questions listed in the EWB subscale had mean scores > 3.00 points, indicating that most women reported higher levels of PWB, SFWB, and EWB. Among all 37 item-specific questions (score range: 0–4 points with

Table 1 Selected characteristics of a sample of Black breast cancer survivors enrolled in the Women's Circle of Health Follow-Up Study (WCHFS), by allostatic load (AL) measure group

Sociodemographics	AL-lipid/metabolic profile-based measure ($n = 229$)	AL-inflammatory profile-based measure ($n = 409$)
	n (%)	*n* (%)
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		
Body mass index (kg/m2), mean±SD	32.7±7.05	32.05±7.03
Body mass index (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)

Table 1 (continued)

Sociodemographics	AL-lipid/metabolic profile-based measure ($n = 229$)	AL-inflammatory profile-based measure ($n = 409$)
	n (%)	*n* (%)
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)
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)
Estrogen receptor (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)
Pre-diagnostic AL score and biomarkers (continuous)	Mean ± SD	Mean ± SD
AL score[b,c]	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
Pre-diagnostic AL score and biomarkers (dichotomized)	Mean ± SD	Mean ± SD
AL score[b,c]		
Low (0–3 points)	149 (65.1)	227 (55.5)
High (4–8 points)	80 (34.9)	182 (44.5)
Systolic blood pressure ≥ 140 mmHg		
Yes	79 (34.5)	120 (29.3)

Table 1 (continued)

Sociodemographics	AL-lipid/metabolic profile-based measure ($n = 229$)	AL-inflammatory profile-based measure ($n = 409$)
	n (%)	*n* (%)
No	150 (65.5)	289 (70.7)
Diastolic blood pressure ≥ 90 mmHg		
Yes	40 (17.5)	64 (15.6)
No	189 (82.5)	345 (84.4)
High-density lipoprotein <50 mg/dL		
Yes	66 (28.8)	–
No	163 (71.2)	–
Low-density lipoprotein ≥ 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 low-density lipoprotein[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)
Estimated glomerular filtration rate, < 59 ml/min		
Yes	–	38 (9.3)
No	–	371 (90.7)
Reproductive characteristics and medical history		
Body mass index (kg/m^2), mean ± SD	32.71 ± 7.05	32.05 ± 7.03
Body mass index ≥ 30 kg/m^2		
Yes	–	228 (55.8)
No	–	181 (44.2)

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

[a]History of breastfeeding was assessed among parous women only

[b]The AL-lipid/metabolic profile-based measure 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]The AL-inflammatory profile-based measure was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, estimated glomerular filtration rate, body mass index, and use of medication to control hypertension, hypercholesterolemia, or diabetes

[d]Abnormal total cholesterol or low-density lipoprotein was defined as: (1) total cholesterol > 240 mg/dL or (2) total cholesterol ≤ 240 mg/dL and low-density lipoprotein > 130 mg/dL

Table 2 Item-specific, subscale and derived total health-related quality of life (HRQOL) scores assessed by Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) instrument in a sample of Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), AL-lipid/metabolic profile-based measure group

Item-specific scores	Overall ($n = 229$) Mean ± SD	Low AL (149) Mean ± SD	High AL ($n = 90$) Mean ± SD	*P* value
Physical well-being (PWB)				
PWB1: lack of energy	2.42 ± 1.19	2.43 ± 1.24	2.41 ± 1.10	0.87
PWB2: have nausea	3.73 ± 0.59	3.75 ± 0.55	3.68 ± 0.67	0.45
PWB3: meet family needs	3.36 ± 1.06	3.41 ± 1.01	3.27 ± 1.15	0.36
PWB4: have pain	2.68 ± 1.31	2.73 ± 1.28	2.58 ± 1.38	0.42
PWB5: bothered by side effects	3.03 ± 1.32	3.04 ± 1.30	3.00 ± 1.36	0.82
PWB6: feel ill	3.49 ± 0.94	3.51 ± 0.90	3.46 ± 1.01	0.70
PWB7: spend time in bed	3.41 ± 1.06	3.44 ± 1.01	3.34 ± 1.15	0.51
Social & family well-being (SFWB)				
SFWB1: feel close to friends	2.96 ± 1.19	2.91 ± 1.20	3.05 ± 1.18	0.41
SFWB2: get emotional support	3.47 ± 0.88	3.43 ± 0.93	3.53 ± 0.80	0.42
SFWB3: have supportive friends	3.26 ± 1.06	3.24 ± 1.05	3.30 ± 1.09	0.71
SFWB4: illness accepted by family	3.67 ± 0.77	3.70 ± 0.72	3.60 ± 0.85	0.33
SFWB5: family communication	3.54 ± 0.95	3.54 ± 0.94	3.54 ± 0.99	0.94
SFWB6: feel close to partner	3.50 ± 1.00	3.49 ± 1.00	3.53 ± 1.01	0.78
SFWB7: satisfied with sex life	2.51 ± 1.62	2.66 ± 1.58	2.21 ± 1.66	0.069
Emotional well-being (EWB)				
EWB1: feel sad	3.05 ± 1.13	3.05 ± 1.16	3.06 ± 1.09	0.92
EWB2: satisfied with coping strategy	3.25 ± 1.02	3.22 ± 1.00	3.30 ± 1.07	0.54
EWB3: lose hope	3.79 ± 0.69	3.83 ± 0.53	3.72 ± 0.92	0.33
EWB4: feel nervous	3.39 ± 0.94	3.44 ± 0.88	3.30 ± 1.04	0.30
EWB5: worry about dying	3.45 ± 0.95	3.45 ± 0.94	3.46 ± 0.97	0.98
EWB6: worry about worsening condition	3.33 ± 1.00	3.32 ± 1.01	3.35 ± 1.00	0.80
Functional well-being (FWB)				
FWB1: able to work	3.07 ± 1.25	3.15 ± 1.22	2.94 ± 1.31	0.23
FWB2: fulfilling work	2.92 ± 1.25	3.03 ± 1.19	2.72 ± 1.36	0.081
FWB3: able to enjoy life	3.27 ± 0.96	3.27 ± 0.97	3.27 ± 0.96	0.99
FWB4: have accepted illness	3.62 ± 0.87	3.64 ± 0.84	3.58 ± 0.93	0.61
FWB5: good sleep quality	2.44 ± 1.37	2.47 ± 1.30	2.39 ± 1.50	0.67
FWB6: enjoy fun things	2.81 ± 1.27	2.87 ± 1.22	2.71 ± 1.34	0.36
FWB7: content with quality of life	2.78 ± 1.28	2.86 ± 1.20	2.65 ± 1.43	0.24
Breast cancer-specific (BCS)				
BCS1: shortness of breath	3.30 ± 0.97	3.33 ± 0.94	3.25 ± 1.03	0.56
BCS2: self-conscious about dressing	2.98 ± 1.46	3.01 ± 1.45	2.92 ± 1.47	0.68
BCS3: swollen or tender arms	3.24 ± 1.23	3.25 ± 1.16	3.23 ± 1.35	0.91
BCS4: feel sexually attractive	2.33 ± 1.40	2.34 ± 1.39	2.33 ± 1.44	0.99
BCS5: bothered by hair loss	2.99 ± 1.47	3.12 ± 1.37	2.73 ± 1.62	0.057
BCS6: worry about family members	2.43 ± 1.41	2.39 ± 1.39	2.52 ± 1.45	0.50
BCS7: worry about the effect of stress	2.52 ± 1.44	2.44 ± 1.39	2.66 ± 1.53	0.28
BCS8: bothered by weight change	2.34 ± 1.57	2.56 ± 1.51	1.92 ± 1.59	**0.0034**
BCS9: feel like a woman	3.28 ± 1.02	3.32 ± 0.97	3.22 ± 1.12	0.46
BCS10: have certain painful parts	2.29 ± 1.34	2.26 ± 1.28	2.34 ± 1.46	0.68
Subscale and derived total scores	Mean ± SD	Mean ± SD	Mean ± SD	*P* value
PWB subscale score (0–28)	22.10 ± 5.10	22.31 ± 4.84	21.73 ± 5.55	0.42
SFWB subscale score (0–28)	23.04 ± 4.79	23.10 ± 4.77	22.92 ± 4.86	0.79
EWB subscale score (0–24)	20.27 ± 3.94	20.31 ± 3.82	20.20 ± 4.19	0.85
FWB subscale score (0–28)	20.92 ± 5.87	21.29 ± 5.79	20.23 ± 6.00	0.19
BCS subscale score (0–40)	27.73 ± 7.01	28.03 ± 6.79	27.16 ± 7.41	0.37
Derived total TOI score (0–96)	70.76 ± 15.65	71.63 ± 15.32	69.12 ± 16.21	0.56
Derived total FACT-G score (0–108)	86.33 ± 15.81	87.00 ± 15.57	85.08 ± 16.27	0.38

Table 2 (continued)

Item-specific scores	Overall ($n=229$) Mean ± SD	Low AL (149) Mean ± SD	High AL ($n=90$) Mean ± SD	*P* value
Derived total FACT-B score (0–148)	114.06 ± 21.43	115.04 ± 21.19	112.24 ± 21.90	0.72

The AL-lipid/metabolic profile-based measure 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

Note Bold *P* value indicated statistical significance using t-test

AL allostatic load, *SD* standard deviation, *TOI* total outcome index, *FACT-G* Functional Assessment of Cancer Therapy-General

a higher score indicating better HRQOL), the question about "losing hope" in the EWB subscale had the highest overall item-specific score of 3.79 ± 0.69 points. This finding suggests that most WCHFS participants remained positive and hopeful after BC diagnosis. In contrast, the lowest 3 overall item-specific scores were all observed in the BCS subscale, and mean scores were 2.33 ± 1.40 points (about sexual attractiveness), 2.34 ± 1.57 points (about weight change), and 2.29 ± 1.34 points (about pain), respectively. With respect to subscale and derived total HRQOL scores, mean scores were generally higher among women with lower AL compared to women with higher AL. Although some lower item-specific scores were observed among women with lower AL-lipid/metabolic profile-based measure, the differences were minimal. It is worth noting that the mean value of the question related to weight change was 0.64 points higher among women with lower AL than those with higher AL, and the difference was statistically significant ($P=0.0034$).

Table 3 depicts descriptive statistics of HRQOL scores in women with AL-inflammatory profile-based measure data. Given that women with AL-lipid/metabolic profile-based measure was a subset of women with AL-inflammatory profile-based measure data, as shown, most HRQOL measures were similar between women in the AL-lipid/metabolic profile-based measure group (shown in Table 2) and women in the AL-inflammatory profile-based measure group (shown in Table 3). In terms of item-specific measures, most questions in the FWB and BCS subscales had an average score between 2.00 and 3.00 points (e.g., fair-good HRQOL measure) compared with the EWB subscale that all 7 item-specific questions had an average score of 3 points or higher, which was indicative of a good–excellent HRQOL measure. With regard to the summed subscale scores, and among subscales with same score range (e.g., 0–28 points), the FWB subscale had a lower average score compared with PWB and SFWB subscales. With respect to the mean HRQOL score difference between lower AL and higher AL among women in the AL-inflammatory profile-based measure group, the mean score differences appeared to be statistically significant for 7 item-specific questions (2 PWB questions, 1 SFWB question, 1 FWB question, and 3 BCS questions) and the PWB subscale score.

Associations of AL with HRQOL

Table 4 shows the univariable and multivariable-adjusted associations of pre-diagnostic AL scores with the post-diagnostic HRQOL measures of interest. In the multivariable-adjusted analysis, we found that among women with a higher AL-inflammatory profile-based measure score, compared to those with a lower score, there were 63% increased odds of having lower FWB (OR 1.63, 95% CI 1.04 to 2.56). Among women with higher AL-inflammatory profile-based measure score, there were 62% increased odds of having lower FACT-G score (OR 1.62, 95% CI 1.04 to 2.54). Similar associations were observed between pre-diagnostic AL-lipid/metabolic profile-based measure and FWB (OR 1.45, 95% CI 0.81 to 2.59) and FACT-G (OR 1.33, 95% CI 0.75 to 2.37), but these findings did not reach statistical significance likely due to limited sample size. Sensitivity analysis suggested that among women in the AL-inflammatory profile-based measure group, the average FWB score was 1.31 points lower in women with higher AL (vs. lower AL) ($P=0.049$). No statistically significant associations were observed between the AL-lipid/metabolic profile-based measure and any of the HRQOL measures (data not shown).

Discussion

In this study, we found that higher AL score using the AL-inflammatory profile-based measure was associated with poorer HRQOL approximately 2 years post-diagnosis among Black BC survivors based on associations with lower FWB and FACT-G scores. While the associations for the AL-lipid/metabolic profile measure were generally similar in magnitude, this measure of AL was not found to be significantly associated with HRQOL, possibly due to limited sample size. The 2-year post-diagnostic HRQOL concerns reported by WCHFS participants were generally related to pain, sex, lack of energy, mental distress, and poor sleep

Table 3 Item-specific, subscale and derived total health-related quality of life (HRQOL) scores assessed by Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) instrument in a sample of Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), AL-inflammatory profile-based measure group

Item-specific scores	Overall ($n = 409$) Mean ± SD	Lower AL ($n = 227$) Mean ± SD	Higher AL ($n = 182$) Mean ± SD	P value
Physical well-being (PWB)				
PWB1: lack of energy	2.42 ± 1.21	2.48 ± 1.23	2.34 ± 1.19	0.26
PWB2: have nausea	3.68 ± 0.72	3.77 ± 0.59	3.57 ± 0.84	**0.0065**
PWB3: meet family needs	3.38 ± 1.06	3.47 ± 0.96	3.27 ± 1.16	0.060
PWB4: have pain	2.70 ± 1.32	2.88 ± 1.24	2.48 ± 1.37	**0.0020**
PWB5: bothered by side effects	2.99 ± 1.34	3.01 ± 1.34	2.97 ± 1.35	0.75
PWB6: feel ill	3.47 ± 0.95	3.54 ± 0.89	3.38 ± 1.02	0.10
PWB7: spend time in bed	3.40 ± 1.05	3.46 ± 0.96	3.32 ± 1.16	0.19
Social & family well-being (SFWB)				
SFWB1: feel close to friends	2.98 ± 1.17	2.98 ± 1.17	2.98 ± 1.18	> 0.99
SFWB2: get emotional support	3.40 ± 0.97	3.42 ± 0.96	3.38 ± 0.99	0.63
SFWB3: have supportive friends	3.21 ± 1.10	3.20 ± 1.12	3.23 ± 1.07	0.78
SFWB4: illness accepted by family	3.67 ± 0.75	3.74 ± 0.69	3.58 ± 0.80	**0.036**
SFWB5: family communication	3.50 ± 0.98	3.53 ± 0.99	3.47 ± 0.97	0.53
SFWB6: feel close to partner	3.49 ± 0.98	3.48 ± 0.99	3.50 ± 0.97	0.84
SFWB7: satisfied with sex life	2.46 ± 1.56	2.48 ± 1.53	2.44 ± 1.61	0.82
Emotional well-being (EWB)				
EWB1: feel sad	3.05 ± 1.16	3.06 ± 1.18	3.04 ± 1.14	0.87
EWB2: satisfied with coping strategy	3.16 ± 1.10	3.14 ± 1.10	3.18 ± 1.09	0.71
EWB3: lose hope	3.77 ± 0.70	3.79 ± 0.64	3.75 ± 0.77	0.58
EWB4: feel nervous	3.36 ± 0.98	3.35 ± 0.97	3.38 ± 1.00	0.77
EWB5: worry about dying	3.41 ± 1.01	3.35 ± 1.01	3.48 ± 1.01	0.18
EWB6: worry about worsening condition	3.26 ± 1.03	3.18 ± 1.10	3.37 ± 0.92	0.067
Functional well-being (FWB)				
FWB1: able to work	3.12 ± 1.23	3.29 ± 1.15	2.90 ± 1.29	**0.0011**
FWB2: fulfilling work	2.84 ± 1.26	2.93 ± 1.24	2.73 ± 1.29	0.12
FWB3: able to enjoy life	3.29 ± 0.95	3.31 ± 0.95	3.27 ± 0.96	0.68
FWB4: have accepted illness	3.56 ± 0.90	3.58 ± 0.86	3.54 ± 0.96	0.59
FWB5: good sleep quality	2.44 ± 1.38	2.46 ± 1.35	2.42 ± 1.41	0.78
FWB6: enjoy fun things	2.83 ± 1.28	2.94 ± 1.23	2.70 ± 1.34	0.065
FWB7: content with quality of life	2.75 ± 1.30	2.84 ± 1.23	2.62 ± 1.38	0.091
Breast cancer-specific (BCS)				
BCS1: shortness of breath	3.32 ± 1.02	3.40 ± 0.96	3.23 ± 1.08	0.097
BCS2: self-conscious about dressing	2.93 ± 1.44	2.92 ± 1.44	2.94 ± 1.44	0.86
BCS3: swollen or tender arms	3.28 ± 1.19	3.36 ± 1.10	3.18 ± 1.30	0.14
BCS4: feel sexually attractive	2.33 ± 1.44	2.45 ± 1.39	2.17 ± 1.49	**0.049**
BCS5: bothered by hair loss	3.12 ± 1.40	3.12 ± 1.39	3.11 ± 1.42	0.96
BCS6: worry about family members	2.37 ± 1.44	2.23 ± 1.41	2.54 ± 1.45	**0.029**
BCS7: worry about the effect of stress	2.39 ± 1.48	2.28 ± 1.48	2.52 ± 1.47	0.095
BCS8: bothered by weight change	2.34 ± 1.57	2.37 ± 1.58	2.30 ± 1.58	0.67
BCS9: feel like a woman	3.20 ± 1.08	3.22 ± 1.04	3.19 ± 1.12	0.77
BCS10: have certain painful parts	2.27 ± 1.34	2.41 ± 1.28	2.10 ± 1.39	**0.022**
Subscale and derived total scores	Mean ± SD	Mean ± SD	Mean ± SD	P value
PWB subscale score (0–28)	22.03 ± 5.23	22.60 ± 4.82	21.32 ± 5.62	**0.015**
SFWB subscale score (0–28)	22.82 ± 5.02	22.89 ± 5.01	22.74 ± 5.05	0.75
EWB subscale score (0–24)	20.01 ± 4.21	19.87 ± 4.31	20.20 ± 4.09	0.43
FWB subscale score (0–28)	20.80 ± 6.06	21.32 ± 6.01	20.15 ± 6.07	0.052

Table 3 (continued)

Item-specific scores	Overall ($n = 409$) Mean ± SD	Lower AL ($n = 227$) Mean ± SD	Higher AL ($n = 182$) Mean ± SD	*P* value
BCS subscale score (0–40)	27.56 ± 7.17	27.77 ± 7.11	27.30 ± 7.26	0.51
Derived total TOI score (0–96)	70.39 ± 16.04	71.69 ± 15.63	68.77 ± 16.44	0.068
Derived total FACT-G score (0–108)	85.80 ± 16.63	86.93 ± 16.40	84.40 ± 16.84	0.12
Derived total FACT-B score (0–148)	113.22 ± 22.38	114.45 ± 22.33	111.70 ± 22.41	0.22

AL-inflammatory profile-based measure was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, estimated glomerular filtration rate, body mass index, and use of medication to control hypertension, hypercholesterolemia, or diabetes

Note Bold *P* value indicated statistical significance using t-test

FACT-B Functional Assessment of Cancer Therapy-Breast Cancer, *AL* allostatic load, *SD* standard deviation, *TOI* total outcome index, *FACT-G* Functional Assessment of Cancer Therapy-General

quality. While WCHFS participants reported similar PWB scores as those reported in a large population-based sample of U.S. cancer survivors [32], they had higher SFWB scores, which is consistent with the literature [33]. EWB and FWB subscale scores were also higher in WCHFS compared with cancer survivors in the general population, however, the differences were not as remarkable as the difference observed for SFWB. Our results also demonstrated that the proportions of item-specific questions with mean scores < 2.50 points were remarkably higher for the BCS subscale compared with all other subscales. This finding might indicate that WCHFS participants tended to be more satisfied with general HRQOL components, but less so with BC-specific HRQOL measures.

To date, most HRQOL research in BC survivors has focused on mental health and sleep problems using validated instruments (e.g., Center for Epidemiological Studies-Depression, Pittsburgh Sleep Quality Index). Unlike other validated HRQOL instruments, FACT-B is especially designed for BC survivors and is more sensitive in capturing BC-related changes [27]. Observational studies using FACT-B scales have shown that Black BC survivors were more likely to experience worse PWB and SFWB [34, 35]. In contrast, data suggest that Black BC survivors report better EWB compared to women belonging to other racial/ethnic groups [36]. In our study, the average score for all item-specific questions related to EWB was > 3.00 points, which suggested higher emotional wellness among WCHFS participants, which is consistent with the literature. However, it is worth noting that EWB for most U.S. BC survivors has declined over time [37]. Thus, it will be important to continue to track EWB among WCHFS participants longitudinally.

Higher AL, based on the inflammatory profile-based measure, was associated with increased odds of poorer FWB and there are various explanations that might support this finding. First, sleep quality is a component of the FWB subscale, and poor sleep quality has been frequently reported by BC survivors [18–20]. Circadian disruption caused by poor sleep quality could have detrimental effects on overall HRQOL and may disturb normal neurophysiological function. Impaired neurophysiological function can affect cumulative physiological stress by increasing circulating pro-inflammatory cytokines, insulin, and cortisol concentrations, which are associated with increased AL [38], and thereby might contribute to poorer HRQOL [38, 39]. We also observed a suggestion of an inverse association between pre-diagnostic AL and HRQOL measured by the BCS subscale, although this finding did not reach statistical significance.

Our a priori hypothesis was that higher pre-diagnostic AL is associated with significantly lower BCS subscale score; however, we did not observe this association. The descriptive data showed that many questions related to BCS concerns had lower scores compared with questions in other FACT-G subscales. This suggests greater variability in the BCS subscale (and less variability in the other subscales) among WCHFS participants. Although no statistically significant associations were observed between higher pre-diagnostic AL and lower BCS subscale score or total FACT-B score among WCHFS participants, the lack of associations may be due to the relatively small sample size which limited our statistical power. Likewise, this study also demonstrated a lack of association between pre-diagnostic AL with HRQOL measured by TOI, which might be because not all WCHSF participants underwent chemotherapy (51.5% and 51.3% of the AL-lipid/metabolic profile-based measure group and AL-inflammatory profile-based measure group, respectively, received chemotherapy). Okuyama et al. [40] concluded that the TOI has limited ability to evaluate HRQOL among all BC survivors, given that it primarily targets those who received chemotherapy.

Strong spiritual and social support from faith-based groups and church families may have positive effects on SFWB and EWB among Black BC survivors [41–43]. However, spiritual and social support is unlikely to impact most

Table 4 Univariable and multivariable logistic regression analyses of the associations between higher pre-diagnostic allostatic load (AL) and lower health-related quality of life (HRQOL) scores assessed by Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) instrument in a sample of Black breast cancer survivors in the Women's Circle of Health Follow-Up Study (WCHFS), by AL measure group

Subscales and derived total scores[c]	AL-lipid/metabolic profile-based measure[a] ($n=229$)		AL-inflammatory profile-based measure[b] ($n=409$)	
	OR (95% CI)		OR (95% CI)	
	Univariable	Multivariable	Univariable	Multivariable
PWB: Low (<23) vs. High (≥23)				
AL score				
Low (0–3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4–8)	0.97 (0.56,1.68)	0.93 (0.52,1.69)	1.40 (0.95, 2.09)	1.49 (0.94, 2.34)
	$P=0.91$	$P=0.61$	$P=0.22$	$P=0.83$
SFWB: Low (<24) vs. High (≥24)				
AL score				
Low (0–3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4–8)	1.24 (0.72, 2.14)	1.21 (0.68, 2.14)	1.08 (0.73,1.59)	1.08 (0.69,1.68)
	$P=0.44$	$P=0.52$	$P=0.71$	$P=0.74$
EWB: Low (<22 for AL 1; <21 for AL 2) vs. High (≥22 for AL 1; ≥21 for AL 2)				
AL score				
Low (0–3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4–8)	0.90 (0.52, 1.56)	1.04 (0.58, 1.87)	0.96 (0.64, 1.42)	1.27 (0.81, 2.02)
	$P=0.71$	$P=0.90$	$P=0.82$	$P=0.30$
FWB: Low (<22) vs. High (≥22)				
AL score				
Low (0–3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4–8)	1.53 (0.88, 2.65)	1.45 (0.81, 2.59)	**1.59 (1.07, 2.36)**	**1.63 (1.04, 2.56)**
	$P=0.13$	$P=0.21$	$P=\mathbf{0.021}$	$P=\mathbf{0.032}$
BCS: Low (<28) vs. High (≥28)				
AL score				
Low (0–3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4–8)	1.31 (0.76, 2.27)	1.44 (0.81, 2.59)	1.13 (0.76, 1.68)	1.36 (0.86, 2.14)
	$P=0.33$	$P=0.22$	$P=0.54$	$P=0.18$
TOI: Low (<73) vs. High (≥73)				
AL score				
Low (0–3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4–8)	1.24 (0.72, 2.13)	1.25 (0.70, 2.23)	1.29 (0.87, 1.91)	1.50 (0.96, 2.34)
	$P=0.45$	$P=0.45$	$P=0.20$	$P=0.08$
FACT-G: Low (<89) vs. High (≥89)				
AL score				
Low (0–3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4–8)	1.34 (0.77, 2.31)	1.33 (0.75, 2.37)	**1.52 (1.02, 2.25)**	**1.62 (1.04, 2.54)**
	$P=0.30$	$P=0.33$	$\boldsymbol{P=0.038}$	$\boldsymbol{P=0.033}$
FACT-B: Low (<117) vs. High (≥117)				
AL score				
Low (0–3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
High (4–8)	1.08 (0.63, 1.87)	1.13 (0.64, 2.01)	1.19 (0.80, 1.76)	1.36 (0.87, 2.13)
	$P=0.78$	$P=0.68$	$P=0.39$	$P=0.18$

Note Bold values indicated statistical significance

OR odds ratio, *CI* confidence interval, *PWB* physical well-being, *SFWB* social & family well-being, *EWB,* emotional well-being, *FWB* functional well-being, *BCS* breast cancer-specific, *TOI* total outcome index, *FACT-G* Functional Assessment of Cancer Therapy-General

The following confounders were included in the multivariable-adjusted analysis: (1) age at diagnosis, (2) birthplace, (3) marital status, (4) menopausal status, (5) family history of breast cancer and (6) number of comorbidities

The median score for AL-lipid/metabolic profile-based measure group and AL-inflammatory profile-based measure group was 3. Thus, 3 was used as the cut-point to dichotomize the AL measure variables (lower

Table 4 (continued)

AL, 0–3; higher AL, 4–8)

[a]AL-lipid/metabolic profile-based measure 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]AL-inflammatory profile-based measure was computed based on the following biomarkers: systolic blood pressure, diastolic blood pressure, waist circumference, glucose level, albumin, estimated glomerular filtration rate, body mass index, and use of medication to control hypertension, hypercholesterolemia, or diabetes

[c]Subscale and derived total scores were dichotomized using median scores as cut-offs

BCS concerns, such as swollen arms, hair loss, and sexual attractiveness. Ashing-Giwa et al. [43] suggested that church is the primary source of support among Black BC survivors, who usually hold stronger religious and spiritual beliefs compared to other women in the U.S. Thus, differences in HRQOL based on scores from FACT-B subscales observed in this study might be explained by strong religious and spiritual beliefs among Black BC survivors. Higher cumulative stress, measured by pre-diagnostic AL, was shown to be a significant predictor of FWB in this study. Furthermore, we found positive, yet not statistically significant, associations between higher pre-diagnostic AL with lower PWB, SFWB, EWB, BCS, TOI, and FACT-B scores. Although HRQOL was assessed using the validated FACT-B instrument, findings from this study should be interpreted with caution due to the relatively small sample Black BC survivors included in our analysis, which may or may not be generalizable to all Black women with BC.

We recognize that using alternative computation methods to estimate AL scores could yield observations and/or interpretations that differ from our current findings, which is a limitation. The relatively small sample size is also an obvious limitation given that most AL-HRQOL associations in our study did not reach statistical significance and had wide CIs. The choice to dichotomize all FACT-B subscales and derived total scores in our analysis is another limitation as it could reduce the potential for comparing our results to those of other investigators, although using binary FACT-B outcome variables was preferred as it allows for ease of interpretation of highly skewed data observed among WCHFS participants. Relatedly, the definition of "poorer HRQOL" may differ by statistical methods, even if all studies followed the same scoring guidelines. However, the observation of left-skewed FACT-B measures in our study was consistent with previous data [36, 44, 45].

Despite these limitations, the major strength of this study is that it was the first study to examine the association of pre-diagnostic AL with HRQOL among Black women, who tend to experience higher cumulative physiological stress [46] and lower HRQOL following BC diagnosis [2, 47, 48]. Our assessment of pre-diagnostic AL as the exposure of interest, afforded by the longitudinal data source and medical records linkage, is also a strength. FACT-B is validated for measuring HRQOL among women with BC (although not validated among Black survivors specifically), hence, factors that mainly affect BC survivors are accounted for. Given that WCHFS is a longitudinal study with detailed data collected at multiple time points, future analysis that includes a larger sample can be prioritized to clarify the preliminary findings reported herein, as well as to determine changes in FACT-B scores over time.

In summary, higher pre-diagnostic AL using the inflammatory profile-based measure was associated with poorer HRQOL among Black women. This study contributes to the limited research on the potential consequences of higher cumulative physiological stress among Black BC survivors (before diagnosis), with a major focus on HRQOL. While not all FACT-B subscales were found to be associated with pre-diagnostic AL in this study, we observed significant inverse relationships between higher AL (using the inflammatory-based measure) with poorer FWB and lower FACT-G scores, but similar although non-significant associations when using the lipid/metabolic profile-based measure. Of note, the AL-inflammatory-based index might be preferable for large-scale, population-based studies given the increased availability of necessary data elements in electronic medical records. Our findings are useful for understanding mechanisms contributing to poorer HRQOL among Black BC survivors and serve as a first step towards clarifying the role chronic physiologic stress plays in long-term HRQOL among BC survivors. Future steps should include validating the current findings and identifying factors that impact AL. In so doing, validated measures of pre-diagnostic AL, may prove helpful for identifying cancer survivors who are at risk for impaired HRQOL and who might benefit from tailored survivorship care. Further, our findings might also inform the development and implementation of targeted preventive strategies to improve AL and HRQOL among Black BC survivors in the near future.

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Compliance with ethical standards

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

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