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EPIDEMIOLOGY

Allostatic score and its associations with demographics, healthy behaviors, tumor characteristics, and mitochondrial DNA among breast cancer patients

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Abstract

Introduction Allostatic load (AL), a composite index, has been used to capture variation in life-course stresses. However, few studies have been carried out among breast cancer patients.

Methods In this study, we examined the cross-sectional association of AL with demographics, healthy behaviors, tumor characteristics, and mitochondrial DNA copy number in breast cancer patients. The study used a sub-sample of 934 women with newly diagnosed breast cancer at M.D. Anderson from 2013 to 2018. To construct the AL score, the study used a battery of seventeen factors that represents the activity of five physiological systems: metabolic, cardiovascular, immunological, renal, and liver.

Results AL was positively associated with the age of disease diagnosis (P = 0.002), and was higher in Black and Hispanic populations than White (P = 0.001 and 0.032, respectively). AL was also found more abundant in those who experienced marital dissolution (P = 0.006), lacked a college education (P = 0.045), currently smoked (P = 0.011), and had low levels of physical activity (P = 0.037) than their counterparts. The study then found that higher AL was associated with increased odds of having poorly differentiated tumors (Odds ratio (OR): 1.40, 95% confidence interval (CI): 1.28, 1.62). An additional significant association was observed between AL with estrogen receptor negative (ER-) (OR = 1.56, 95%CI: 1.02, 2.36) among Black patients. Finally, we observed a significant positive correlation between AL with leukocyte mitochondrial DNA copy number variation (P < 0.001).

Conclusions We conclude AL is influenced by selected demographics and healthy behaviors, and further is correlated with tumor characteristics and mitochondrial DNA copy number in breast cancer patients.

Keywords Allostatic load · Breast cancer · Social-demographics · Healthy behaviors · Tumor characteristics

Introduction

It has been well-regarded that individuals with lower socioeconomics status (SES) are more likely to develop chronic diseases in their lifetime [1]. Low SES is associated with breast cancers' aggressive tumor characteristics that appear with increased frequency among Black women in past years. The characteristics include high grade, late stage at diagnosis, and estrogen receptor-negative status [2], all of which may contribute to racial disparities in breast cancer outcomes [3, 4]. The robustness of these associations and the fact that SES appears important for the large majority of disease outcomes suggests that there may exist a common mechanism underlying the pathogenies of various disease types. One potential candidate is chronic stress, which can damage biological systems directly (e.g. circulating glucocorticoids) and indirectly via its effects on other biobehavioral risk factors (e.g. smoking, alcohol consumption, physical activity) that are known to impinge upon health.

In the United States, compared to White women, Black and Hispanic women are more likely to have increased levels

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of psychosocial stressors during their lifetime [5–7]. Therefore, the cumulative exposure to higher life course stressors among Black and Hispanic women may increase the likelihood of disrupting the physiological regulatory systems that involve the whole process of the stress response. This disruption will lead to larger deterioration and eventually increase the women's risks of breast cancer, the likelihood of developing more aggressive breast tumor phenotypes, and shortened survival [8]. Social gradients are intricately involved in various biological factors related to stress response [8]. Allostatic load (AL) score, an index that includes cardiovascular, metabolic, immunological, and neuroendocrine components – that has been used to estimate stress-induced biological risk [8]. Although no gold-standard measure is available [9, 10], AL is socially patterned [11–14] and independently foresees morbidity, symptom, and mortality of age-related diseases [15, 16].

Among biological systems commonly assessed in AL score, several of them, including metabolic and immunological systems, play roles in breast carcinogenesis [17–21]. For example, obesity is associated with an increased risk of postmenopausal breast cancer and reduced survival [22]. Therefore, it is likely that AL may predict breast cancer risk and outcomes. Unfortunately, to date, only a couple of studies have assessed the association of AL with breast cancer [10]. In a recent study, Xing et al. reported that higher AL was associated with poorer tumor grade and larger tumor size in Black breast cancer patients [23]. Thus, though still very limited, the evidence suggests that AL is implicated in breast cancer.

In this study, we used a total of 17 factors that represent the activity of 5 different physiological systems to construct the AL score: metabolic, cardiovascular, immunological, renal, and liver. These factors were selected based on reports from prior literature [14, 23–28], and the data quality and availability of relevant factors in our study sample. Given the potential role of AL in implanting adverse life experience into biological systems, we specifically attempted to investigate the associations between the AL score at the time of disease diagnosis and selected demographics, healthy behaviors, and aggressive breast tumor characteristics in 934 women with newly diagnosed stage I to III breast cancer at M.D. Anderson from 2013 to 2018. Our hypothesis stated that adverse demographics and unhealthy behaviors are associated with increased AL, and elevated AL is associated with the more aggressive breast tumor characteristics. In addition, we examined the association between AL and leukocyte mitochondrial DNA copy number variation. As shown in a systemic review by Martin et al. [29], both acute and chronic stressors could impact mitochondrial biology. Our hypothesis was that mitochondrial is involved in the process of AL biologically embedding.

Materials and Methods

Study population

The study participants were selected from an ongoing breast cancer study beginning in 2012. Participants were patients at The University of Texas M. D. Anderson Cancer Center (Houston, TX) with newly diagnosed (defined by the presence of malignant breast epithelial cells) and histologically confirmed stage I to III (by microscopic analysis and molecular subtype) breast cancer. Blood samples were drawn prior to any cancer treatment. Written informed consent was obtained from each study participant. Self-reported ethnic background was used to define race and ethnicity. This study was approved by the Institutional Review Boards of M.D. Anderson Cancer Center and all study participants provided written informed consent prior to the baseline interview.

Data sources and factors used to construct AL score

Data used in the analysis were collected from interviews, medical records, and laboratory assays. The in-person, interviewer-administered questionnaires were conducted at the time of cancer diagnosis, which included demographic, 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. Through these measurements, we obtained three factors, namely waist circumference, body mass index (BMI), and history of taking medication to control metabolic diseases and hypertension, which were all included in AL. Medical records were obtained from M.D. Anderson institutional electronic medical record and updated every 6 months after the time of disease diagnosis. Laboratory testing data relevant to the estimation of the primary exposure, AL, were abstracted from the time of disease diagnosis and prior to any treatment. From laboratory testing data, we extracted 12 factors, including Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), High Density Lipoprotein (HDL), Low Density Lipoprotein (HDL), total cholesterol, triglycerides, blood glucose, blood HbA1C, serum albumin, estimated glomerular filtration rate (eGFR), creatinine, and resting heart rate (RHR), all of which were included in the AL score. Laboratory assay for inflammatory cytokines: Serum C-Reactive Protein (CRP) was measured using ELISA Kit (Cat No. CYT298, Millipore) and Serum Interleukin 6 (IL-6) was measured using ELISA Kit (Cat No. EZHIL6, Millipore). Standard curves were generated following the Manufacturer's instructions. Both positive and negative controls were included in every plate. To adjust batch effect, a control serum from one donor was used as controls on all of the

plates. As of the start of the analysis, 934 breast cancer cases had the relevant data abstracted from their medical records and available for analysis.

Aggressive breast tumor characteristics (outcome variables)

Information on tumor characteristics was available from medical and pathology records, and "aggressive" tumor characteristics were defined on the basis of four clinicopathologic characteristics: (1) ER status: negative (-) vs positive (+); (2) tumor stage: late (III) vs early (I&II); (3) tumor grade: poorly (grade 3) vs moderately and well differentiated (grade 1/2); (4) tumor size: large (≥ 2 cm) vs small (< 2 cm).

AL score construction

We used a total of 17 factors to construct AL score. They are SBP, DBP, HDL, LDL, total cholesterol, triglycerides, waist circumference, BMI, glucose, HbA1C, albumin, estimated glomerular filtration rate (eGFR), creatinine, CRP, IL-6, RHR, and the history of taking medication to control metabolic diseases and hypertension. We combined LDL and total cholesterol together to generate a new factor, named "abnormal cholesterol". Cases with total cholesterol > 240 mg/dL or total cholesterol ≥ 240 mg/dL and LDL > 130 mg/dL were deemed to have abnormal cholesterol. Thus, our AL score actually included 16 factors. Various methods have been used to construct AL scores [9, 10, 14, 23–25, 30, 31]. In this study, we used a cutoff value to assign each variable a threshold of risk that determined the score (0 or 1) that each variable 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): (1) SBP ≥ 140 mmHg; (2) DBP ≥ 90 mmHg; (3) HDL < 50 mg/dL; (4) total cholesterol > 240 mg/dL or total cholesterol ≥ 240 mg/dL and LDL > 130 mg/dL; (5) triglycerides ≥ 150 mg/dL; (6) waist circumference ≥ 88 cm; (7) BMI ≥ 30; (8) glucose level ≥ 110 mg/dL; (9) HbA1C > 6.5; (10) albumin < 4 g/dL; (11) CRP > 3 mg/L; (12) IL-6 > 1.8 pg/mL; (13) eGFR < 60 mL/min/1.73m^2; (14) Creatinine > 1.2 mg/dL; (15) RHR > 100 bpm; (16) previously taking medications to control metabolic diseases and hypertension. Then, points were summed to obtain a continuous measure for AL score, each with maximum possible score of 16 (range: 0–16). The score was then dichotomized using the median of the score as the cutoff (median. 8 points; lower AL, 0–8 points; higher AL, 9–16 points).

Determination of mitochondrial DNA copy number

We used a real-time quantitative polymerase chain reaction (PCR) to determine mitochondrial DNA copy number. This method, which has high interassay reliability, is detailed in our previous publications [32–34]. A diluted reference DNA, a negative control DNA, and a calibrator DNA were included in each run to generate the standard curves. For each sample, the assay was run in duplicate.

Statistical analysis

Descriptive statistics (frequencies and percentages) were calculated to describe the demographics, healthy behaviors, medical history, and tumor characteristics of our study population. First, we evaluated whether AL score (continuous variable) differed by demographics, healthy behaviors, and tumor characteristics (categorical variables). The Student t test was used to assess the difference. To account for the influence of age of diagnosis and race, we applied linear regression analysis with the adjustment of age of disease diagnosis and race. To clarify the association between AL and race, we applied linear regression analysis with the adjustment of age at diagnosis, marital status, education, smoking status, alcohol status, physical activity, and tumor stage. Potential interactions between AL with those covariates were assessed. Then, we assessed the relationship between higher AL (categorical variable) and aggressive tumor characteristics using logistic regression analysis. Adjusted variables included age at diagnosis and race, as appropriate. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated in logistic regression analysis. To further identify race-specific association, we performed stratified analysis by race. Finally, spearman correlation analysis was applied to evaluate the correlation between AL score (continuous variable) with mitochondrial DNA copy number. 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

This study included a total of 934 breast cancer cases. Table 1 illustrates the distributions of demographics, healthy behaviors, and tumor characteristics. The average age of disease diagnosis was 53.7 years old, and about a third of cases diagnosed were younger than 50 years old. Approximately seventy percent of patients were White, and twenty prevent were Black. Nearly half of the cases were married or living together, and slightly over forty percent had less than college-level education. In terms of healthy behaviors, a half were never smokers, a quarter were never drinkers,

Table 1 Demographics, healthy behaviors, and tumor characteristics in breast cancer patients

Variable	Breast cancer cases (n = 934), n (%)
Age at diagnosis (years)	
20–49	302 (32.33)
50–59	295 (31.59)
60 +	337 (36.08)
Race	
Whites	651 (69.70)
Blacks	177 (18.95)
Hispanics	106 (11.35)
Marital status	
Married or living together	461 (49.36)
Single/never married	275 (29.44)
Separated/divorced/widowed	198 (21.20)
Education	
College graduate/and above	233 (24.95)
Technical school/some college	309 (33.08)
Below college	392 (41.97)
Smoking status	
Never	473 (50.64)
Former	349 (37.37)
Current	112 (11.99)
Alcohol drinking	
Never	249 (26.66)
Former	451 (48.29)
Current	234 (25.05)
Physical activity	
High	182 (19.49)
Medium	260 (27.84)
Low	492 (53.68)
ER status	
ER+	658 (70.45)
ER−	276 (29.55)
Tumor stage	
I/II	605 (64.78)
III	329 (35.22)
Tumor grade	
Well differentiated	197 (21.09)
Moderately differentiated	285 (30.51)
Poorly differentiated	452 (48.39)
Tumor size	
< 2 cm	591 (63.28)
≥ 2 cm	343 (36.72)

and a half had low levels of physical activity. For clinical and tumor characteristics, nearly 30% had ER- tumors, two-thirds were diagnosed with stage I/II tumors, and half had poorly differentiated tumors. Also, over a third were diagnosed with tumors at least 2 cm large.

A total of 17 factors were used, including SBP, DBP, HDL, LDL, total cholesterol, triglycerides, waist circumference, BMI, blood glucose, HbA1C, and creatinine, serum albumin, CRP, and IL-6, RHR, eGFR, and a history of medication controlling metabolic diseases and hypertension. With respect to individual biomarkers initially reported as continuous variables, predetermined cutoff points were applied to categorize the patients into high and low-risk groups (Table 2). Over a third of cases had elevated SBP, and 20% had elevated DBP. About one third had an abnormal HDL or total cholesterol (with or without LDL), or both. Approximately 86% of patients had a waist circumference of at least 88 cm, and more than half had obesity. About 30% had elevated blood glucose and serum albumin levels, and over a half had elevated HbA1C. Around a half had higher serum CRP and IL-6 levels. In terms of eGFR, 11% had an increased risk. Around 10% had abnormal RHR and creatinine levels. Using questionnaire data, we found about 60% had a history of taking medication to control metabolic diseases (e.g., diabetes and hypercholesterolemia) and hypertension.

Overall, the average computed AL score was 7.44 in all study participants (Table 3). The score ranged from 0 to 15, suggesting that there were no women who fell into the high-risk category for all 16 factors used in the computation of AL score. We investigated whether AL differed by demographics, healthy behaviors, and tumor characteristics. AL was positively associated with the age of disease diagnosis ($P = 0.002$). Compared to those younger than 50, those diagnosed between 50 to 59 and at least 60 years old had higher AL levels (7.72, 7.83 vs. 6.73; $P < 0.001$, respectively). Black and Hispanic cases had higher AL levels than White patients (8.31, 7.91 vs. 7.21; $P < 0.001$ and 0.014, respectively). A significant difference was observed between those who experienced marital dissolution (separated, divorced, or widow) and those who married or living together (7.76 vs. 7.22, $P < 0.001$). AL did not differ by levels of education. For healthy behaviors, AL was higher in current smokers than those who had never smoked (8.00 vs. 7.24, $P = 0.005$). AL did not differ by alcohol drinking status and levels of physical activity. And AL did not differ significantly by any of those tumor characteristics.

To account for the influence of age and race, we reanalyzed the associations mentioned above in a linear regression analysis with the adjustment of age of diagnosis and race (Table 3). The significant associations observed in the univariate analysis remained. Additional significant associations were observed. Compared to those with at least a college education, those without a college education had higher AL (7.76 vs. 7.22, $P = 0.045$). Those with low physical activity levels had higher AL than those with increased physical activity levels (7.54 vs. 7.12, $P = 0.037$). Finally, those with poorly differentiated tumors had higher AL than

Table 2 Distribution and high-risk cut points for individual biomarkers of AL scores

Biomarkers	Mean (SD)	Cutoff value	N (%) at risk
SBP (mm Hg)	135.78 (15.47)	≥ 140	356 (38.12)
DBP (mm Hg)	80.24 (10.05)	≥ 90	198 (21.20)
HDL (mg/dL)	62.78 (19.26)	< 50	302 (32.33)
LDL (mg/dL)	126.73 (98.72)	> 130	224 (23.98)
Total cholesterol (mg/dL)	185.47 (31.45)	≥ 240	256 (27.41)
Triglycerides (mg/ dL)	99.76 (48.29)	≥ 150	106 (11.35)
Waist circumference (cm)	101.86 (19.45)	≥ 88	801 (85.76)
BMI (kg/M^2)	31.17 (6.03)	≥ 30	544 (58.24)
Glucose level (mg/dL)	78.46 (25.48)	≥ 110	283 (30.30)
HbA1C (mg/dL)	7.2 (3.7)	> 6.5	529 (56.64)
Albumin (g/dL)	4.25 (2.79)	< 4	295 (31.58)
CRP (mg/L)	2.02 (3.47)	> 3	548 (58.67)
IL-6 (pg/mL)	1.42 (2.84)	> 1.8	439 (46.89)
eGFR (mL/min/1.73m^2)	92 (10.4)	< 60	81 (8.67%)
Creatinine (mg/dL)	0.82 (0.35)	> 1.2	102 (10.92)
RHR (bpm)	69 (34)	> 100	87 (9.31)
History of medication to control metabolic diseases and hypertension	Yes	Yes	689 (60.49)

those with well-differentiated ones (7.62 vs. 7.20, P = 0.042). In addition, we reanalyzed the association between AL and race with the adjustment of the age at diagnosis, marital status, education, smoking status, alcohol status, physical activity, and tumor stage. AL was still higher among Black (P = 0.006) and Hispanic (P = 0.038) cases.

Next, we assessed the relationship between higher AL as a categorical variable and aggressive breast tumor characteristics, including ER negative, high tumor stage (III), poorly differentiated tumor grade, and large tumor (≥ 2 cm) (Table 4). For all cases, a significant association was only observed between high AL and having poorly differentiated tumors (OR = 1.40, 95%CI; 1.28, 1.62). When further stratified by race, the significant association between high AL and having poorly differentiated tumors was consistently observed in White (OR = 1.37, 95%CI; 1.14, 1.70), Black (OR = 1.57, 95%CI; 1.11, 2.40), and Hispanic (OR = 1.65, 95%CI; 1.01, 2.77) cases. In addition, significant associations were observed between high AL with having ER- breast tumors (OR = 1.56, 95%CI; 1.02, 2.36) among Black cases only.

Finally, we correlated AL with mitochondrial DNA copy number in leukocytes (Table 5). We found that increased AL was associated with increased levels of mitochondrial DNA copy number. The correlation coefficients (Rho) were 0.126 (P < 0.001) for all study participants, and 0.114 (P = 0.009), 0.130 (P = 0.011), and 0.147 (P = 0.021) for White, Black, and Hispanic participants. Then, we reassessed the association between higher AL and poorly differentiated tumor grade by including mitochondrial DNA copy number as a covariable. Mitochondrial DNA copy number was dichotomized using median levels into two groups: low and high. We found the significant association between higher AL and having poorly differentiated tumors was lessened (OR = 1.21, 95%CI: 1.05, 1.40) when mitochondrial DNA copy number was added into the model. This may suggest that mitochondrial is one of the molecular targets of AL. In addition, a higher mitochondrial DNA copy number was found associated with increased odds of having poorly differentiated tumors (OR = 1.30, 95%CI: 1.14, 1.50).

Discussion

In this study, we hypothesized that AL, a putative sub-clinical measure of physiological dysregulation across multiple organ systems, is a potential process or mechanism through which the social environment becomes biologically embedded into the tissues and organs of the body to precipitate the stressors of those of adverse experience [9, 10, 14, 23–25, 30, 31]. We further hypothesized that mitochondria are involved in AL biologically embedding process. Given Black and Hispanic women in the United States are more likely to experience higher levels of stressors during their lifetime than white women, it would be noteworthy to explore how stressors may affect AL and consequently lead to the observed racial disparities in breast cancer, namely aggressive tumor characteristics and reduced survival among Black and Hispanic breast cancer patients.

Table 3 AL score by demographics, healthy behaviors, and tumor characteristics

Variable	AL score (SD)	P value	P value*
AL score (continuous)	7.44 (2.40)		
Age at diagnosis (years)			
20–49	6.73 (2.83)	Reference	Reference
50–59	7.72 (2.98)	< 0.001	0.012
60 +	7.83 (2.69)	< 0.001	0.011
Race			
Whites	7.21 (2.52)	Reference	Reference
Blacks	8.31 (2.82)	< 0.001	0.001
Hispanics	7.91 (3.53)	0.014	0.032
Marital status			
Married or living together	7.22 (3.11)	Reference	Reference
Single/never married	7.58 (3.09)	0.128	0.196
Separated/divorced/widowed	7.76 (3.27)	< 0.001	0.006
Education			
College graduate/and above	7.24 (3.14)	Reference	Reference
Technical school/some college	7.36 (2.98)	0.650	0.469
Below college	7.62 (2.45)	0.093	0.045
Smoking status			
Never	7.24 (2.28)	Reference	Reference
Former	7.53 (2.92)	0.110	0.138
Current	8.00 (3.45)	0.005	0.011
Alcohol drinking			
Never	7.35 (3.29)	Reference	Reference
Former	7.49 (2.91)	0.561	0.479
Current	7.44 (3.14)	0.755	0.362
Physical activity			
High	7.12 (3.63)	Reference	Reference
Medium	7.47 (3.08)	0.276	0.252
Low	7.54 (2.17)	0.068	0.037
ER status			
ER+	7.35 (1.98)	Reference	Reference
ER−	7.65 (2.99)	0.072	0.056
Tumor stage			
I/II	7.39 (2.84)	Reference	Reference
III	7.53 (3.45)	0.506	0.482
Tumor grade			
Well differentiated	7.20 (3.47)	Reference	Reference
Moderately differentiated	7.32 (3.06)	0.689	0.528
Poorly differentiated	7.62 (2.74)	0.099	0.042
Tumor size			
< 2 cm	7.38 (2.39)	Reference	Reference
≥ 2 cm	7.54 (2.78)	0.354	0.405

*Adjusted by age and race as appropriate

In this study, we found that AL was positively associated with the age of disease diagnosis (P = 0.002) and significantly higher among Black and Hispanic patients than White patients (P = 0.001 and 0.032, respectively). Additionally, AL was affected by both demographics (e.g., marriage status and education) and healthy behaviors (cigarette smoking status and physical activity). In relation to aggressive tumor characteristics, higher AL was associated with increased odds of having poorer tumor differentiation in all cases and having ER- breast tumors in Black patients. In further analysis, we noted that leukocyte mitochondrial DNA copy number was positively correlated with AL and may partially mediate the association between higher AL and poorer tumor differentiation. These findings have provided strong evidence to support AL's potential role in linking social adversity with breast cancer outcomes and racial disparities.

Though AL score is constructed differently across the studies, it usually includes factors associated with cardiovascular, metabolic, immunological, and neuroendocrine components [9, 10, 14, 23–25, 30, 31]. In this study, a panel of 17 factors representing the activity of 5 different physiological systems: cardiovascular (SBP, DBP, and RHR), metabolic (HDL, total cholesterol, triglyceride, waist circumference, BMI, HbA1c, and glucose), immunological (CRP and IL6), renal (Creatinine and eGFR), and liver (Albumin) were used to construct the AL score. To account for the confounding from medication on cardiometabolic function, we included the history of taking medication to metabolic diseases and hypertension extracted from the questionnaire as a factor in AL. One weakness in our AL score is that we did not include any factor related to the neuroendocrine system, such as norepinephrine and epinephrine, because we could not measure them in our study. In a recent study, stress-induced epinephrine was found to enhance lactate dehydrogenase A and promote breast cancer stem-like cells [35].

Social support is perhaps the essential cause of health differentials. In agreement with this statement, the study found that AL was higher in those who were divorced, widowed, or separated (P = 0.006) than those married or living together. Our results are consistent with other studies [36, 37]. In a recent study by Tobin et al., Black women of ages 18–69 years who experienced marital dissolution (divorced, widowed, or separated) had higher AL than those who married or never married [36]. However, this kind of association was not observed among White women. In another study among old adults, Rote et al. found that married individuals also have significantly lower AL scores than those who are widowed [37]. Additionally, we found that AL was higher in those without a college-level education (P = 0.045) than those with at least a college degree. This is expected because AL is inversely correlated with education levels, a major component of socioeconomic status (SES).

In relation to healthy behaviors, we found that AL was higher among those who currently smoked and had low levels of physical activity than those who never smoked and

Table 4 Multivariate analysis to assess associations between AL score category and aggressive breast tumor characteristics at baseline by race

	All (n = 934) OR (95%CI)*	Whites (n = 651) OR (95%CI)*	Blacks (n = 177) OR (95%CI)*	Hispanics (n = 106) OR (95%CI)*
ER status: negative vs positive	1.14 (0.96, 1.27)	1.06 (0.77, 1.41)	1.56 (1.02, 2.36)	1.34 (0.73, 4.99)
P value	0.236	0.719	0.037	0.424
Stage: III vs I/II	1.08 (0.82, 1.34)	1.05 (0.81, 1.46)	1.07 (0.64, 2.14)	1.08 (0.60, 3.50)
P value	0.652	0.758	0.837tes	0.874
Grade: poorly vs well or moderate differentiated	1.40 (1.28, 1.62)	1.37 (1.14, 1.70)	1.57 (1.11, 2.40)	1.65 (1.01, 2.77)
P value	< 0.001	0.091	0.022	0.047
Size: ≥ 2 cm vs < 2 cm	1.15 (0.88, 1.40)	1.15 (0.84, 1.43)	1.17 (0.82, 2.27)	1.08 (0.59, 2.41)
P value	0.275	0.307	0.557	0.841

*Adjusted by age at diagnosis and as appropriate

Table 5 Correlations between AL score with mitochondrial DNA copy number in leukocytes

	All (Rho (P value)	White, Rho (P value)	Black, Rho (P value)	Hispanics, Rho (P value)
AL	0.126 (< 0.001)	0.114 (0.009)	0.130 (0.011)	0.147 (0.021)

had high levels of physical activity (P = 0.011 and 0.037, respectively). Unhealthy behaviors, including smoking, excessive drinking, disturbed sleep, and physical inactivity, can promote and exacerbate pathophysiology by dysregulating key biological processes, such as inflammation [38, 39]. A number of studies support the link between smoking and high AL [40–44]. However, Petrovic et al. found that smoking is not associated with high AL [45]. Several studies identified that higher physical activity is associated with a decrease in AL [46–50]. Thus, our results are consistent with the literature reports. A few studies have shown that moderate alcohol consumption has beneficial effects in lowering AL in men and women [51–53]. In our study, we did not observe a similar association. We did not collect sleep information in our study, so the association between AL and sleep cannot be assessed.

In consistent with other reports from the United States [10, 24, 26, 31, 50, 54, 55], higher AL was observed in Black and Hispanic patients than White patients. In addition to the fact that Black and Hispanic populations have higher prevalence of hypertension, obesity, diabetes, liver disease and renal dysfunction than White populations [56–60], the racial difference in AL is likely to have social determinants. Racial inequalities in SES have been well-documented in the United States [31, 61, 62] and lower individual SES has been long known inversely associated with AL [8, 12]. In our study, lower education was found associated with higher AL, but the racial difference in AL was not explained by education. This might be due to the lack of statistical power, given the association between education and AL in our study is relatively weak, and the number of Black and Hispanic cases included in this study is modest. It may also suggest that there exist other factors that contribute to the racial difference in AL. Geronimus et al. found that non-poor Black women reported higher AL scores than poor White women [31]. In our study, we only evaluated SES factors (education, income, and health insurance) at individual level. The potential influence of neighborhood factors was not assessed. Those factors could include neighborhood deprivation and racial segregation, which have been found to contribute the observed racial difference in AL. For example, in Black women, Tan et al. reported that neighborhood disadvantage, but not education level or household income, was significantly associated with AL [63]. Bellatorre et al. in NHANES [64] found racial segregation as a significant predictor of AL as well.

In this study, we found that higher AL was associated with 1.40-fold increased odds of having poorly differentiated tumors. Tumor grade is one of the best-established prognostic factors in breast cancer [65]. High tumor grade predicts early recurrence and progression, metastasis, and short survival. Thus, our results may suggest that higher AL is associated with worse clinical outcomes in breast cancer patients. We also found the association between higher AL and having poorly differentiated tumors differed by race. The association was stronger in Black and Hispanic patients than White (P = 0.015). The underlying mechanism contributing to this racial difference is unclear. Black and Hispanic women are known to be likely diagnosed with aggressive breast tumors [66, 67]. Interestingly, in a previous study by Parente et al., the association between AL and breast cancer risk was only observed in Black women but not in White women. Thus, it is possible that the impact of AL on breast tumor characteristics differs by race. To support this assumption, we found that higher AL was associated with increased odds of having ER- breast tumors only among Black patients, not among White and Hispanic patients. Black women are more likely to develop ER- breast tumors than their White counterparts,

so it is possible that higher AL in Black women may contribute to the high prevalence of ER- breast tumors among them. Our findings are consistent with a previous report that higher AL scores were associated with increased odds of having poorer tumor differentiation in Black breast cancer patients [23], though AL scores were constructed differently. Unfortunately, their study only included Black women. The racial difference observed in our study cannot be confirmed in their study.

To further explore the impact of AL at the cellular level, we evaluated the associations between AL with mitochondrial DNA copy number. Significant positive correlations were observed for AL and mitochondrial DNA copy number in all three races. We further found that mtDNA copy number could partially mediate the relationship between Al and aggressive breast tumor characteristics. Our findings are consistent with the notion that acute and chronic stressors influence various aspects of mitochondrial biology and that chronic stress exposure can lead to molecular and functional recalibrations among mitochondria. The main function of mitochondria is to produce energy and against oxidative stress, which commonly occurs in stress response. High levels of stress, as indicated by increased AL, will lead to elevated oxidative stress and oxidative DNA damage in mitochondrial DNAs, which will result in mitochondrial dysfunction. To maintain the normal cellular function, cells will have to activate the feedback system and produce more copies of normal mitochondria. That is probably why we observed the positive association between increased Al with increased mitochondrial DNA copy number. An increase in mitochondrial DNA copy number has been found to be associated with a wide range of psychological stress, including childhood parental loss, abuse, maltreatment, and a wide range of stressful events over one's lifetime [68, 69]. The consistency may raise a possibility that the biologically embedding process of AL targets mitochondrial. Clearly, functional studies are needed to further clarify the role of mitochondrial in AL.

There are some limitations to this study. Various methods have been used to construct AL score in the literature [9, 10, 14, 23–25, 30, 31]. Thus, it is not out of the question that using an alternative method to estimate AL scores could produce different results. However, we included 17 different factors representing five major physiological systems, which are almost always included in other studies. Thus, we are confident that our AL score will represent the human body's response well. The minority population in our study is modest, so we may not have adequate power to detect certain race-specific associations. Another limitation is the AL measure itself. As suggested by McCrory and her colleague, AL, may only reflect adverse social events that happened during adulthood, but not during childhood [14]. Early life events, particularly adverse events, may play a role in breast carcinogenesis [70].

The considerable strengths of our study outweigh the limitations. Our approach of addressing our research question by utilizing data available through collection and abstraction of medical and pathology records, as well as through interviewer-administered questionnaires, sets an example for future similar studies to explore the relationship between AL with cancer risk and outcomes. In addition, by including Black and Hispanic cases, we could assess research questions related to breast cancer racial disparities. In summary, we carried out the first study to evaluate the role of AL in relation to social-demographics, healthy behaviors, and tumor characteristics in a multi-ethnic breast cancer patient cohort. Findings from this study contribute important knowledge on factors that might be related to racial disparity in breast cancer. Additional research with large sample sizes is needed to validate the results, particularly with the inclusion of SES factors at individual and neighborhood levels. In addition, basic scientific research is warranted to delineate the biological pathways AL may be involved in and further clarify the role of mitochondrial in AL-related pathways.

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Data sharing The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

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

Ethical approval All procedures performed in this study were approved by the Institutional Review Board at M D Anderson Cancer Center and in accordance with the ethical standards of 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all participants.

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