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Allostatic Load and Breast Cancer: a Systematic Review of the Literature

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Abstract

Purpose of the Review This systematic literature review aims to synthesize the existing literature on allostatic load and breast cancer.

Recent Findings Eight articles met the study inclusion criteria. Study results suggest high allostatic load is associated with poorly differentiated tumors and Black race among women with a history of breast cancer. Additionally, psychosocial support and exercise appear to be avenues to reduce allostatic load. Unfortunately, the relationship between allostatic load and tumor size, hormone receptor status, and patient-reported outcomes, i.e., health-related quality of life, are unclear and warrant further investigation.

Summary Allostatic load is emerging as an essential biological correlate of stress among patients with breast cancer. Future studies should further delineate its role across the breast cancer continuum from oncogenesis through survivorship.

Keywords Allostatic load · Stress · Allostatic overload · Breast cancer

Introduction

Allostatic Load and Stress Overview

Stress is a part of modern-day life. Stressors may be internal, external, acute, or chronic. Humans are usually well adapted to acute stress [1]. Chronic stress, however, deprives individuals of biological homeostasis [2]. Extensive work by McEwen and colleagues suggests chronic activation of the stress pathway—hypothalamic–pituitary–adrenal axis (HPA) and the sympathetic adrenal nervous system (SAM) may result in disease initiation and progression [3–8].

The concept of allostatic load (AL) provides a framework to understand the physiologic implications of chronic exposure to physical or psychological environmental stress [9]. AL is related to homeostasis and allostasis. Homeostasis describes health as a state where all physiological parameters must function within unchanging setpoints [10]. The principle of allostasis refers to the idea that resting levels of stress hormones adapt or adjust to experiences over time [11]. Unlike physiological systems such as body temperature, which are homeostatic systems that must be maintained within a relatively narrow range of values, resting levels of stress hormones have a relatively broad plausible range [7]. When stress is chronic and ongoing, stress response systems are under allostatic load [4, 6]. They are understood to adapt by altering resting-state set points to relatively high levels and are therefore not flexibly regulated [12]. AL is the "wear and tear" resulting from chronic overactivity or inactivity of physiological systems adapting to environmental challenges [13].

Allostatic Load Calculation

Traditionally, AL has been computed using the ten biomarkers first published by Seeman and colleagues [3]. The markers can be divided into primary mediators, secondary,

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and tertiary outcomes [6]. Primary mediators are chemical messengers released as part of allostasis [6]. Secondary outcomes are integrated processes that reflect the cumulative effects in a specific tissue or organ in response to the primary mediator [6]. Tertiary outcomes are the resultant morbidity from physiologic dysregulation [6]. Examples of primary mediators are cortisol, dehydroepiandrosterone sulfate (DHEA), norepinephrine, and epinephrine. Secondary outcomes include systolic and diastolic blood pressure, waist-hip ratio, high-density lipoprotein, total cholesterol, and glycated hemoglobin [6]. Tertiary outcomes comprise chronic illnesses such as diabetes, hypertension, and cancer [6]. These biomarkers and others used in calculating AL serve distinct functional purposes in calculating AL as a measurement for the burden of stress on the body [14].

There are no standard physiologic systems or biomarkers used in calculating AL [15]. AL is calculated by developing an aggregate index of physiological dysfunction represented by biomarkers—anthropometric measurements and clinical laboratory values. In the quartile approach to calculating AL, the biomarkers are divided into quartiles based on their distribution in the study sample. High risk for each biomarker is either the top 25% in the distribution or the bottom 25% of the distribution based on how dysfunction is assessed in the marker. To that extent, heart rate, for example, would be the top 25%, while albumin would be the bottom 25% as these quartiles represent the highest risk [16]. In the quartile approach, each individual is assigned a value of 1 if they are in the high-risk category or a 0 if in the low-risk category for all markers to calculate a total AL value out of 10 [3, 17] or another number depending on how many biomarkers are used. This quartile approach is the most common approach to calculate AL [9]. Other methods to calculate AL include averaging continuous z scores of various biomarkers, clinically relevant cutoffs of biomarkers, or stratifying biomarker data by deciles [18, 19]. The Z score approach may afford a more significant predictive value for the examined outcomes but may not capture the impact of system-specific contributions [20]. Sex-specific high-risk cut points for three individual markers: waist circumference, waist-hip ratio, and high-density lipoprotein cholesterol are sometimes used in studies [18]. The inclusion of medications as evidence of prior or ongoing physiologic dysregulation in AL calculations is controversial. Recommendations include assigning no points, 1 point, or ½ a point for medications [18]. Although the construct validity of AL has been well established, how the biomarkers contribute to AL or how the composite AL functions is an area of active research [21]. A recent paper by Wiley et al. suggests AL functions through a bifactor model where the composite AL accounts for variance in biomarkers, and each physiologic system is representative of variance "over and above AL." [21, 22]. The previously described approaches to calculating AL assume each biomarker equally contributes to the allostatic load score [18].

An alternative measure of AL is Fava et al.'s clinimetric evaluation of allostatic overload. Allostatic overload describes physiologic dysregulation secondary to physical or psychological environmental needs that exceed an individual's coping ability [23•]. The clinimetric evaluation is a two-part instrument administered as a semi-structured interview [24]. The clinimetric assessment examines (1) an identifiable source of stress—the stressor can be an acute life event or chronic stress and (2) clinical manifestations of the stressor, i.e., "*psychological symptoms, impairment in social and occupational functioning,* etc." [24, 25].

Allostatic Load and Breast Cancer

Currently, how chronic stress contributes to diseases such as breast cancer is understudied. Using biomarkers to quantify stressors, including physiologic, psychological, and social burdens, can serve as a means to understand breast cancer oncogenesis, treatment response, and survival [26]. Evidence shows that heightened stress response in breast cancer patients may lead to physiologic changes that influence cancer-related outcomes [27]. In one study, the authors found negative emotional coping styles were linked to adverse effects in women with metastatic breast cancer [28]. Similarly, another study showed depressive symptoms and elevated cortisol were associated with suppressed immunity in women with mestastatic breast cancer [29]. The stress response has also been linked to poorer cancer-related outcomes in patients with breast cancer [30].

Studies have demonstrated that a significant proportion of women with a history of breast cancer have experienced distress at higher levels than the general population [31]. In addition, Black women tend to experience higher health adverse psychosocial stressors than non-Hispanic White women in the USA, leading to potentially more adverse outcomes at all stages of breast cancer [32]. Unfortunately, there is a dearth of literature on the relationship between AL, operationalized as a biological correlate of stress, and breast cancer. This review seeks to synthesize the literature on AL among breast cancer patients, present the state of the research, ascertain gaps in the literature, and identify opportunities for more research.

Methods

Search Strategy

This study followed the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. [33] Computer-based searches were

conducted in the following academic databases: (1) PubMed [Cancer subset]; (2) MEDLINE, (3) PsycINFO; and (4) CINAHL. To maximize search results, we used various combinations of keywords found in the literature and Medical Subject Heading (MeSH) terms related to cancer and allostatic load. Each database was searched with the keywords *cancer* or *neoplasm* in combination with keywords to capture allostatic load, such as allostasis and "multi-systemic biological risk." A complete list of search terms can be found in Table 1.

Study Selection

We conducted a systematic search for qualitative and quantitative empirical studies that reported findings on allostatic load and cancer. To be included, study outcomes needed to be related to allostatic load among breast cancer patients or patients at risk for breast cancer. In addition, we were interested in studies taking place both within the USA and internationally. Lastly, we limited our review to peer-reviewed studies published in English.

Three reviewers individually assessed the relevance of each study. Any disagreements between reviewers were reconciled by consensus. We used a two-step inclusion process. In step 1, we examined article titles and abstracts and excluded articles that clearly did not have a focus on breast cancer, allostatic load, or that were not empirical. However, we erred on the side of inclusion when the study focus was unclear. In step 2, the full text of the citations was retrieved and examined for all remaining studies that were not excluded in phase 1. The full text articles of the remaining citations were obtained for independent assessment of all inclusion criteria.

Data Extraction and Analysis

We systematically extracted the following information from each of the papers included in our review: study design, cancer stage, allostatic load measures, study outcomes. This information was collated and thematically analyzed. Using thematic analysis, we also examined the literature and the extent to which AL was used in the context of breast cancer and identified gaps that can be explored in future research.

Results

Our keyword search identified an initial yield of 255 citations. After removing duplicates, there were 137 non-duplicative citations. The primary reasons for exclusion can be found in Fig. 1. Eight citations were included in the systematic review after applying the study's exclusion criteria to the titles, abstracts, and full-text citations.

Study Design and Population Characteristics

Of the eight studies meeting criteria for this review, most were cohort or cross-sectional studies examining large national [34, 35], statewide [36, 37], or institutional databases [38, 39]. Two studies were randomized control trials evaluating the impact of an intervention, i.e., physical activity [40] or supportive-expressive group therapy [41] on allostatic load. All the studies only examined women, and the majority were conducted within the USA. A significant number of articles focused exclusively on Black women [36, 37, 40]. There were only two international studies [41]. Study outcomes included change in allostatic load score or allostatic load biomarkers [39–41], tumor characteristics (e.g., tumor size) [37, 38], mitochondrial DNA copy number [38], posttraumatic growth [35], and patient-reported outcomes (e.g., health-related quality of life [HRQOL]) [36]. One study focused on women at risk for breast cancer [40], five on women in the survivorship phase of care [34–37], and two on metastatic breast cancer patients [39, 41]. Notably, most studies papers were published within the last 5 years. The studies meeting inclusion criteria are summarized in Table 2.

Allostatic Load Calculation

Only the Abercrombie et al. study focused on individual allostatic load biomarkers. The remaining studies using allostatic load biomarkers calculated a composite allostatic load score. The composite AL scores mainly comprised secondary and tertiary outcomes, with one study using primary mediators. Although the biomarkers used to calculate allostatic load were not uniform across studies, most studies used biomarkers representing the cardiac, immune, and metabolic physiologic systems. In addition to the clinical

Table 1 Operationalization of the search terms

Cancer	cancer OR neoplasms
Allostatic load	"allostatic load" OR "allostatic overload" OR allostasis OR "multi systemic biological risk"

Search terms within each category are combined with OR. Search terms between categories are combined with AND. Some terms were truncated

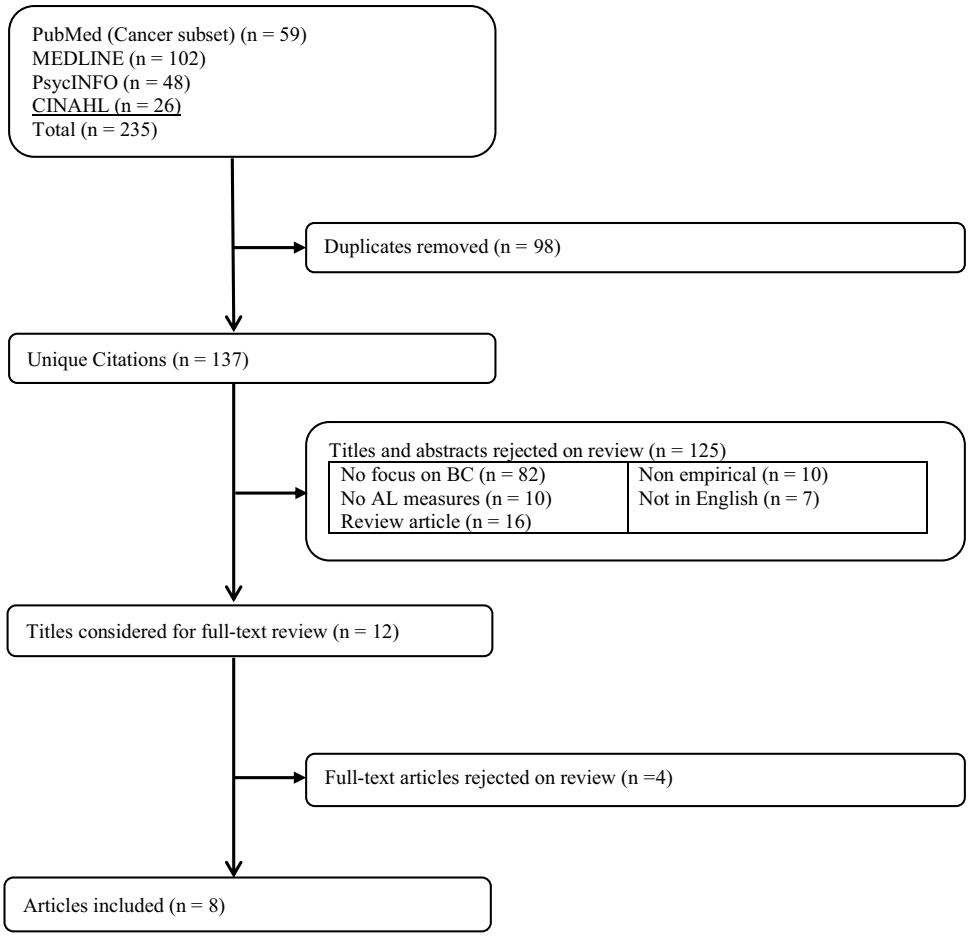

Fig. 1 Flow chart

laboratory values and anthropometric measurements, some studies included medications to control hypertension, diabetes, and hypercholesterolemia in calculating allostatic load [36, 37].

The most frequently used biomarkers to represent the cardiac and metabolic physiologic systems, respectively, are systolic blood pressure, diastolic blood pressure, and body mass index. C-reactive protein was the most commonly used immune biomarker. Notably, Xing et al. created two allostatic load measures—a lipid profile allostatic load and an inflammatory index-based allostatic load. The inflammatory profile had the same biomarkers as the lipid profile with the addition of body mass index (BMI), estimated glomerular filtration rate (eGFR), and albumin [36, 37]. The number of biomarkers used to calculate the composite score across studies ranged from 9 to 17.

There was significant heterogeneity in the time frame allostatic load biomarkers were collected. Biomarkers were collected up to 12 months before diagnosis, at the time of cancer diagnosis, and 9 months post-diagnosis. Additionally, not all biomarkers were collected simultaneously in some studies.

The studies with a composite allostatic load score used established clinical cutoffs to assign points. Specifically, subjects with clinically abnormal values for a biomarker received a point. The biomarkers' points were then totaled into a composite score with an increasing allostatic load score representative of worsening physiologic dysregulation. Adams-Campbell and Ye operationalized allostatic load as a continuous variable, while the remaining studies dichotomized it into high versus low allostatic. Of note, Adams-Campbell standardized allostatic load by creating a Z-score allostatic load score [40].

The Ruini et al. study was the only one to examine allostatic overload using the clinimetric assessment.

Study Outcomes

Tumor Characteristics and Mitochondrial DNA Copy Number

Compared to low allostatic load, high allostatic load was consistently associated with poor tumor differentiation [36, 38]. However, the relationship between allostatic load

Table 2 Summary of Studies on Breast Cancer or Breast Cancer risk and Allostatic (AL)

Author (year)	Study design	Study population	Allostatic load calculation	Key study results
Abercrombie (2004)	Cohort study	48 women—17 metastatic breast cancer patients, 31 controls	1. Waist circumference 2. Diurnal slope of cortisol	Patients with metastatic breast cancer had significantly flatter diurnal cortisol rhythms than did healthy controls Patients with metastatic breast cancer with greater disease severity showed higher mean cortisol levels, smaller waist circumference, and a tendency toward flatter diurnal cortisol rhythms No relationships were found between psychological measures and allostatic load biomarkers in patients with metastatic breast cancer Controls with flatter cortisol rhythms showed larger waist circumference, poorer performance on explicit memory tasks, lower perceived social support, and a tendency toward higher perceived stress
Adams-Campbell (2021)*	Randomized control trial	71 post-menopausal Black women with metabolic syndrome at risk for breast cancer based on the Care Model Study arms: (1) a supervised, facility-based aerobic exercise intervention ($n=73$), (2) a home-based exercise intervention ($n=69$), (3) a control group whose participants were asked to maintain their baseline daily activities for the duration of the study	Cardiac 1. Systolic blood pressure (≥ 130 mmHg) 2. Diastolic blood pressure (≥ 85 mmHg) 3. Triglycerides (≥ 150 mg/dL) 4. HDL (< 50 mg/dL) Metabolic 5. Fasting glucose (? 100 mg/dL) 6. Body mass index (30 kg/m2) 7. Waist circumference (> 88 cm) Immune 8. C-reactive protein (> 10 mg/L)	Reduction in allostatic load in 6 months in both exercise arms compared to the control arms Smoking (current or former), family history of breast cancer, a personal history of hypertension and menopausal symptoms were associated with a high allostatic load compared to no smoking, no family history of breast cancer, no history of hypertension, and no menopausal symptoms Subset analysis showed a reduction in AL among women who had a family history of breast cancer
Parente et. al (2012)	Cross-sectional study	4875 Black and White women, ages 35–85 with a history of breast cancer compared to those with no cancer	Cardiac 1. Systolic blood pressure ≥ 140 mmHg 2. Diastolic blood pressure ≥ 90 mmHg 3. Heart rate ≥ 90 beats; per minute 4. Total cholesterol level ≥ 240 mg/dL 5. High-density lipoprotein cholesterol < 50 mg/dL Metabolic 6. Body mass index ≥ 30 kg2/m 7. Glycosylated hemoglobin ≥ 6.4% 8. Albumin < 4 g/dL Immune 9. C-reactive protein > 3 mg/L AL operationalization: low AI ≤ 3, high AL ≥ 4	History of breast cancer was a predictor of AL score in Black women not White women Black race, older age, lower income, low levels of education, low physical activity, and high alcohol intake were also all predictors of elevated AL levels Interaction analysis between Black race and history of breast cancer was significant
Ruini (35)	Cohort study	120 women—60 women with a prior diagnosis of breast cancer and 60 healthy women	Clinimetric evaluation	Women with a history of breast cancer without allostatic overload had the highest mean post traumatic growth (PTG) and women with a history of breast cancer and allostatic overload had the lowest PTG Women with a history of breast cancer with allostatic overload scored higher on the PTG scales of personal strength and spiritual changes than healthy stressed women with allostatic overload There was no difference in the PTG scales for women with a history of breast cancer or healthy women with stress without allostatic overload

Table 2 (continued)

Author (year)	Study design	Study population	Allostatic load calculation	Key study results
Xing et. Al (2020a)	Cross-sectional, cohort study	409 Black women, ages 20–75	*Lipid profile AL* Cardiac 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 Metabolic 6. Waist circumference ≥ 88 cm 7. Glucose level ≥ 110 mg/dL Tertiary outcomes 8. Ever use of medications to control hypertension, diabetes or hypercholesterolemia *Inflammatory pathway* Cardiac 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 Metabolic 6. Waist circumference ≥ 88 cm 7. Glucose level ≥ 110 mg/dL 8. eGFR < 59 mL/min 9. Albumin < 4 g/dL 10. BMI ≥ 30 kg/m2 Tertiary outcomes 11. Ever use of medications to control hypertension, diabetes, or hypercholesterolemia AL operationalization: low Al 0–3, high AL 4–8	This study defined unfavorable tumor pathology as invasive behavior, higher grade (3 vs 1–2), larger tumor size (< 2 cm vs ≥ 2 cm) and estrogen receptor negative status High AL 1 is associated with poorly differentiated tumors High AL 2 is associated with poorly differentiated tumors and larger tumors No association between AL and invasive disease or receptor status

Table 2 (continued)

Author (year)	Study design	Study population	Allostatic load calculation	Key study results
Xing et. al (2020b)	Cross-sectional, cohort study	409 Black women, ages 20–75	*Lipid profile AL* Cardiac 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 Metabolic 6. Waist circumference ≥ 88 cm 7. Glucose level ≥ 110 mg/dL Tertiary outcomes 8. Ever use of medications to control hypertension, diabetes, or hypercholesterolemia *Inflammatory pathway* Cardiac 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 Metabolic 6. Waist circumference ≥ 88 cm 7. Glucose level ≥ 110 mg/dL 8. eGFR < 59 mL/min 9. Albumin < 4 g/dL 10. BMI ≥ 30 kg/m^2 Tertiary outcomes 11. Ever use of medications to control hypertension, diabetes, or hypercholesterolemia AL operationalization: low Al 0–3, high AL 4–8	High inflammatory profile AL was associated with a lower functional well-being on Functional Assessment of Cancer Therapy-Breast Cancer-B (FACT-B) assessment and low Functional Assessment of Cancer Therapy-General (FACT-G) score Functional well-being on FACT-B and FACT G did not reach statistical significance for the AL lipid profile

Table 2 (continued)

Author (year)	Study design	Study population	Allostatic load calculation	Key study results
Ye (2017)	Randomized controlled trial of a supportive group therapy intervention on AL	226 Chinese patients with metastatic breast cancer—108 intervention group, 104 control group	Cardiac 1. Resting pulse 2. Standard deviation of R-R intervals (heartbeat to heartbeat), 3. Systolic blood pressure and diastolic blood pressure 4. White blood cell count Metabolic 1. Body mass index 2. Waist hip ratio 3. Red blood cell count 4. Hemoglobin Immune 5. C-reactive protein 6. Interleukin-6 7. CD4 + 8. CD8 + Neuroendocrine 9. Serotonin 10. Hormone cortisol	No difference in cancer-specific survival at 3 or 5 years No effect of the BRBC Program on 5-year survival Anxiety and depression: 2 months and 6 months the intervention group had lower rates of anxiety and depression. At 12 months anxiety and depression were stable compared to 6 months Resilience and quality of life (QOL): 2 months resilience in the intervention group increased. QOL and resilience improved at 6 months but were stable at 12 months Allostatic load improved, but the effect size was not significant at 2 months, but at 6 and 12 months it was significant
Zhao et. al (2021)	Cross-sectional	934 Black and White women, aged 20–60+	Cardiac 1. SBP ≥ 140 mmHg 2. DBP ≥ 90 mmHg 3. Heart rate > 100bmp 4. HDL < 50 mg/dL 5. LDL > 130mgdL 6. Total cholesterol > 240 mg/dl 7. Triglycerides ≥ 159 mg/dL Metabolic 8. Waist circumference ≥ 88 cm 9. Body mass index ≥ 30 10. Blood glucose ≥ 110 mg/dL 11. Hemoglobin A1C > 6.5 12. Serum albumin < 4 g/dl 13. eGFR < 60 mL/min/1.73m^2 14. Creatinine > 1.2 mg/dL Immune 15. CRP > 3 mg/L 16. IL-6 1.8 pg/mL Tertiary outcomes 17. Medications to control metabolic disease and hypertension AL operationalization: low 0–8, high 9–16	High AL is associated with low education, Black race, and Hispanic ethnicity High AL associated with smoking and low physical activity In Black women elevated AL is associated with estrogen receptor negative tumors High AL is associated with leukocyte mitochondrial number

*This study created an AL score based on Z-score. The Z-score was derived by summing the standardized AL components

and tumor size was inconsistent. In Xing et al.'s examination of the Women's Circle of Health Follow-up Study (WCHFS), high allostatic load was associated with larger tumors (≥ 2 cm) [36]. Conversely, there was no relationship between allostatic load and tumor size in the institutional cohort evaluated by Zhao et al. [38]. Similarly, the relationship between hormone receptor status and allostatic load is unclear. Some studies suggest an association between Black race, high allostatic load, and estrogen receptor negative status [38] while others found no association [37].

Of note, an increased allostatic load was associated with a high mitochondrial DNA copy number [38]. Furthermore, the relationship between allostatic load and tumor differentiation was attenuated by including mitochondrial DNA copy number on adjusted analysis [38].

Patient-Reported Outcomes

Only one paper examined the relationship between allostatic load and patient-reported outcomes. Results indicate that among Black women in survivorship, there is an association between a high inflammatory-based allostatic load index and lower functional well-being on the Functional Assessment of Cancer Therapy-Breast Cancer-B (FACT-B) and a low Functional Assessment of Cancer Therapy-General (FACT-G) [36]. However, there was no significant relationship between the lipid profile allostatic load measure and any health-related quality of life (HRQOL) measures [36].

Metastatic Breast Cancer

Examining allostatic load biomarkers—cortisol and waist circumference, Abercrombie et al. found patients with metastatic breast cancer had flatter diurnal cortisol than healthy controls [39]. There was no correlation between psychological measures, i.e., perceived stress and social support, and diurnal cortisol or mean cortisol in patients with metastatic breast cancer. Contrarily, lower perceived support was associated with a flatter diurnal cortisol in the healthy controls. Study results also showed patients with worsening metastatic disease had higher mean cortisol and a smaller waist circumference [39].

Ye et al. examined the impact of a supportive group therapy intervention, Be Resilient to Breast Cancer (BRBC), on the allostatic load in Chinese women with metastatic breast cancer. Patients in the BRBC intervention arm experienced a reduction in their allostatic load at 6 months and 12 months compared to the control group [41]. Notably, despite the decrease in allostatic load, the BRBC intervention did not improve 3- or 5-year cancer-specific survival.

Race

Individuals from marginalized and minoritized groups, i.e., Black women and Hispanic women with a history of breast cancer, had a higher allostatic load than White women with a history of breast cancer [38]. Moreover, for Black women, the interaction between Black race and a history of breast cancer increased the probability of a high allostatic load [34]. Conversely, there was no association between a history of breast cancer and high allostatic load in White women [34].

Healthy Behaviors

Adams-Campbell et al. examined the implications of physical activity on reducing allostatic load among women at risk of breast cancer. The study focused on post-menopausal Black women with metabolic syndrome at risk for breast cancer based on the CARE Model. Study results suggest supervised facility-based aerobic exercise or home-based exercise reduced allostatic load over the 6-month study period compared to baseline daily activity in the control group [40]. Moreover, poor health behaviors such as smoking were associated with a high allostatic load. These results on health behaviors are consistent with studies in patients with a history of breast cancer where high allostatic load was associated with smoking and low physical activity [38].

Post-Traumatic Growth (PTG)

One study examined allostatic overload and post-traumatic growth (PTG) in women with a history of breast cancer versus healthy stressed women. The study cohort examining PTG was divided into four groups—(1) women with a history of breast cancer without allostatic overload, (2) women with a history of breast cancer with allostatic overload, (3) healthy stressed women with allostatic overload, and (4) healthy stressed women without allostatic overload. For the overall PTG score, women with a history of breast cancer without allostatic overload had the highest mean PTG, and women with a history of breast cancer and allostatic overload had the lowest PTG. This finding was not statistically significant. Women with a history of breast cancer with allostatic overload scored higher on the PTG scales of personal strength and spiritual changes than healthy stressed women with allostatic overload. Conversely, there was no difference in the PTG scales for women with a history of breast cancer or healthy women with stress without allostatic overload [35].

Discussion

Our examination of existing studies on AL and breast cancer suggest the literature is still evolving. Additionally, there has been significant growth in studies on AL in patients with breast cancer within the last 7 years [42•]. This review indicates high AL is associated with poorly differentiated tumors and Black race among women with a history of breast cancer. Moreover, psychosocial support and physical activity appear to be avenues to reduce allostatic load. Unfortunately, the relationship between allostatic load and tumor size, hormone receptor status, and patient-reported outcomes, i.e., HRQOL, are unclear and warrant further investigation. Nevertheless, the results from this review confirm AL is a viable biologic correlate for stress and has implications across the breast cancer continuum from diagnosis through survivorship.

The findings on Black race, breast cancer tumor characteristics, and AL are significant as Black race, and unfavorable tumor characteristics have been implicated in poor breast cancer outcomes. Black women with breast cancer are more likely to present with tumors that are larger, poorly differentiated, and estrogen receptor negative than their White counterparts [43–45]. Additionally, Black women with breast cancer have the worst mortality rates of all racial and ethnic groups [45]. In populations with no history of cancer, Black women have a higher AL than White women, White men, and Black Men [46]. Furthermore, Black women with breast cancer face high rates of external stressors such as living in neighborhoods with low socioeconomic status [47], discrimination within the healthcare system [48], and financial hardship [49] than White women with breast cancer. Within this context, findings of an elevated AL among Black women with a history of breast cancer or an association between AL and poorly differentiated tumors are unsurprising. Of note, due to its association with race and adverse social determinants of health, some have advocated for AL to be operationalized as a measure of structural inequity and inequality to better understand racial disparities in breast cancer [50•].

Due to the heterogeneity in the data sources and study designs, calculations of composite AL differed across studies. Most studies were limited by the availability of biomarkers in their respective dataset. Notably, the composite AL score calculations in most studies only used secondary and tertiary outcomes. The omission of primary mediators in composite AL scores is most likely due to their limited use in clinical practice [42•]. Nonetheless, most of the biomarkers used were consistent with the most frequent biomarkers used to calculate AL [15, 18]. The lack of standardized biomarkers used in composite AL scores highlights the need for additional studies to standardize and validate a "gold standard" of biomarkers to calculate AL in breast cancer patients. A validated AL composite score will enable comparisons of the implications of AL in breast cancer patients across studies [50•]. In addition, further studies are needed to understand the effects of the individual AL biomarkers versus the composite AL score on sociodemographic factors, treatment, and clinical outcomes in patients with breast cancer. The role of biomarkers and/or composite AL as a predictor, mediator, or moderator of oncogenesis, tumor progression, and survival needs clarification.

The Ye et al. and Adams-Campbell et al. studies suggest AL is dynamic and can be mitigated with interventions. Avenues to reduce AL are important as elevated AL has been associated with poor oncologic outcomes such as worse overall and disease-specific survival in patients with cancer [42•, 51]. Additionally, the study interventions of psychosocial support through stress reduction [52, 53] and physical activity [54] have been independently associated with decreased breast cancer mortality. Consequently, longitudinal studies examining the trajectories of AL and its implications for breast cancer diagnosis through survivorship are needed. Although Ye et al. examined survival, they did not explicitly examine a reduction in AL as a predictor, moderator, or mediator of survival.

This review underscores many of the gaps in AL and breast cancer research. Firstly, none of the studies examined the relationship between AL and clinical outcomes such as recurrence, overall survival, and breast cancer-specific survival. Secondly, important contributors to prognosis, such as differences in treatment receipt and completion or treatment response, have not been examined. Thirdly, there is a lack of racial and ethnic diversity in many of the populations studied with racial or ethnic groups examined in isolation, incorrectly identified as one racial and ethnic group (e.g., Hispanic) or excluded altogether (American Indian, Pacific Islander, etc.). Other areas for research are comparisons between clinimetric measures of allostatic overload, individual AL biomarkers, or the composite AL score in patients with breast cancer.

This study has some limitations that should be considered. The exclusion of non-English articles may have limited the number and breadth of articles. Additionally, the heterogeneity in study designs and endpoints prevented summarizing study findings in a meta-analysis. The strength of this study is the methodological rigor of how the systematic review was conducted.

Conclusions

Allostatic load is emerging as an essential biological correlate for stress among patients with breast cancer. In addition, it provides a framework to develop and measure the biological effects of socioenvironmental factors on breast cancer diagnosis, treatment, and survival. Ultimately, a comprehensive societal approach that seeks to reduce the incidence and prevalence of environmental and social injustices among historically and intentionally excluded communities will benefit society by reducing stress, thus mitigating its effects on breast cancer oncogenesis through survival.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent Not applicable.

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