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Research Article

Allostatic Load As a Predictor of Recurrence in Patients with estrogen receptor positive Breast Cancer: A Case-Control study

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Abstract:

Background: Allostatic load (AL), a biomarker of chronic stress, has been linked to an increased breast cancer risk, aggressive tumor characteristics, and worse survival among breast cancer patients. However, its role in breast cancer recurrence is unknown.

Materials and Methods: In this nested case-control study, we analyzed the association between AL and breast cancer recurrence among patients who were diagnosed with ER+, HER2-, and stage I to III breast cancer and completed definitive surgery with adjuvant radiation and hormone therapy as the standard of care. The study population included 49 patients who had relapsed after the treatment and 147 patients who had no relapse within three years after cancer treatment.

Results: In the analysis, we found that per one unit increase of AL was associated with a 17% increase in breast cancer recurrence (Odds ratio (OR)=1.17, 95% confidence interval (CI): 1.01, 3.62) after the adjustment of sociodemographic, healthy behavioral, and clinical factors. A significant association was further confirmed in the categorical analysis. Compared to those in the low AL group (AL≤2), those in the higher AL group (AL>2) had a 1.62-fold increased risk of breast cancer recurrence (OR=1.62, 95%CI: 1.02, 5.36).

Conclusion: In brief, the results from this study have presented evidence to support the role of AL in breast cancer recurrence. More research is needed to further confirm the association.

Key words: allostatic load; breast cancer; recurrence

Introduction

About 60-80% of diagnosed breast cancer is estrogen receptor-positive (ER+) [1]. Standard care for ER+ breast cancer includes definitive surgery followed by adjuvant hormone therapy (tamoxifen or an aromatase inhibitor) [2]. Those treatments have significantly improved the clinical outcome of ER+ breast cancer. However, there is still more than a quarter of ER+ breast cancer patients who will recur during their lifetimes [2-4]. Given breast cancer is the most diagnosed cancer among U.S. women [5], the relapse of ER+ breast cancer poses a significant threat to women. Therefore, there is a need to identify ER+ breast cancer patients who are more likely to relapse in the future. Those patients may benefit from additional or other treatments. Allostatic load (AL) is a biomarker of chronic stress [6, 7]. Emerging literature suggests that exposure to adverse socioeconomic status (SES) at individual and neighborhood levels and a history of unhealthy behaviors (e.g., cigarette smoking, being physically inactive, poor sleep quality) is associated with an elevated AL, and consequently an increased risk of developing chronic diseases such as cardiovascular disease, diabetes, cancer, and worse mortality [6, 8-10]. About breast cancer, increased AL has been linked to a higher risk of breast cancer [11, 12], aggressive tumor characteristics (e.g., poorly differentiated tumor grade) [13-15], and all-cause mortality in breast cancer patients [16]. However, none of those studies have assessed the relationship between AL and breast cancer recurrence. Intriguingly, among breast cancer patients, lower SES at the individual level is associated with higher recurrence risk [17]. A history of cigarette smoking

and being physically inactive have been linked to increased breast cancer recurrence [18, 19]. Given lower SES, unhealthy behaviors (e.g., cigarette smoking and physical inactivity) are associated with increased AL [6], it is reasonable to assume that higher AL may increase recurrence risk among breast cancer patients. To test this hypothesis, in this nested case-control study, we analyzed the association between AL at the time of cancer diagnosis and recurrence risk among 196 ER+, HER2-, stage I to III breast cancer patients.

Materials and Methods

Study population

This was a nested case-control study, with cases and controls selected from a breast cancer study whose 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 from October 2012 to June 2015 and followed for recurrence. For this study, we included patients who had been diagnosed with ER+ and HER2- breast cancer and completed definitive surgery and adjuvant radiation and hormone therapy as standard of care. Recurrent cases were defined as having recurred based on the standardized clinical criteria for recurrence-free interval (RFI), which includes invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, distant recurrence, or death from breast cancer. Subjects exited the cohort at the time of relapse. The final assessment was performed in June 2019 to determine the relapse status of every patient. Controls were selected in a 1:3 case/control ratio using cumulative density sampling (also known as survivor sampling) and individually matched on time since diagnosis and chemotherapy status since increasing time since diagnosis is associated with an increased risk of relapsed breast cancer, and chemotherapy has significant implications in recurrence. A total of 49 recurrent cases and 147 controls were identified in this study. The median time to recurrence among cases was 16 months. Blood samples were drawn prior to any cancer treatment, and written informed consent was obtained from each study participant. Self-reported ethnic background was used to define ethnicity. This study was approved by the Institutional Review Boards and all study participants provided written informed consent before the baseline interview.

Data collection and AL score construction

Data used in the analysis were collected from interviews, medical records, and laboratory assays. The procedure of data collection has been detailed previously(11, 13). The in-person, interviewer-administered questionnaires were conducted at the time of cancer diagnosis, including sociodemographic and healthy behavioral factors. We also obtained the information on the status of whether taking any medication to control metabolic diseases and hypertension in the past 12 months, which was included in AL. Medical records were obtained from the institutional electronic medical record (EHR). Anthropometric measurements and laboratory testing data relevant to estimating the primary exposure, AL, were abstracted from the time of disease diagnosis and before any treatment. We extracted factors, including body mass index (BMI), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (HDL), total cholesterol, triglycerides, and blood HbA1C, all of which were included in the AL score. In addition, we included serum C-Reactive Protein (CRP) in the AL measurement [13]. CRP was measured using ELISA Kit (Cat No. CYT298, Millipore). Standard curves were generated following the Manufacturer's instructions. 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. Detailed information on the cutoff value for each factor has been described previously [13]. Distributions of the ten factors contributing to the AL score are shown in **Supplement Table 1**.

Table 1: Distribution of AL scores in the study population

AL score	Number	Percentage
0	45	22.96
1	34	17.35
2	15	7.65
3	25	12.76
4	27	13.78
5	17	8.67
6	16	8.16
7	11	5.61
8	6	3.06
9	0	0.00
10	0	0.00

Then, points were summed to obtain a continuous measure for the AL score, each with a maximum possible score of 10 (range: 0–10). The score was then dichotomized using the median of the score as the cutoff (lower AL, ≤2 points; higher AL, >2 points). Information on tumor characteristics was available from medical and pathology records, including tumor stage: late (III) vs early (I&II); tumor grade: poorly (grade 3) vs moderately and well differentiated (grade 1/2); tumor size: large (>2cm) vs small (≤2cm) [13].

Statistical analysis

First, we compared sociodemographic, healthy behavioral, and clinical variables between recurrence and control groups. The Chi-square test was applied for the categorical variables and the Student T-test was used for

the continuous variable. Then, we assessed the difference in AL in each category of a covariate between the overall case and control groups. We also compared AL across the categories of each covariate within the general study population and case groups. The Student T-test or ANOVA was used to detect the difference between two or more categories for each covariate. To assess the association between AL and breast cancer recurrence, we applied conditional logistic regression, matched on time since diagnosis and status of chemotherapy. Both univariate and multivariate analyses were applied. In the multivariate analysis, we included age, ethnicity, education, smoking status, alcohol drinking, family history of cancer, tumor stage, grade, and tumor size as covariates in the initial model. However, only family history of cancer, tumor stage, and grade were included in the final model because all other covariates were not significant in the model (P>0.20). All statistical analyses were performed using the Stata Statistical Software Package version 18.0 (Stata Corp, College Station, TX).

Results

This study included a total of 196 breast cancer cases, 49 with recurrence and 147 without recurrence. **Table 1** shows the distribution of AL in the study population. Forty-five patients (~23%) had an AL score of 0, indicating no risk factor. Conversely, no patients had more than an AL score of 8. Breast cancer sociodemographic, healthy behavior, and clinical information are shown in **Table 2**.

Table 2: Sociodemographic, healthy behavioral, and clinical factors in cases and controls

Variable	Controls (n=147)	Cases (n=49)
Age of diagnosis, Mean (SD)	55.2 (4.1)	53.8 (7.5)
Ethnicity, n (%)		
Whites	115 (78.23%)	35 (71.43%)
Blacks	17 (11.56%)	10 (20.41%)
Hispanics	15 (10.20%)	4 (8.16%)
Education		
At least College graduate	40 (27.21%)	12 (24.49%)
Below college graduate	107 (72.79%)	37 (75.51%)
Smoking status		
Never	103 (70.07%)	33 (67.35%)
Former/current	44 (29.93%)	16 (32.65%)
Alcohol consumption		
Never	74 (50.34%)	18 (36.73%)
Former/current	73 (49.66%)	31 (63.27%)
Family history of cancer		
No	72 (48.98%)	32 (65.31%)
Yes	75 (51.02%)	17 (34.69%)
Tumor stage		
I/II	117 (79.59%)	32 (65.31%)
III	30 (20.41%)	17 (34.69%)
Tumor grade		
Well/moderately differentiated	110 (74.83%)	30 (61.22%)
poorly differentiated	37 (25.17%)	19 (38.78%)
Tumor size		
≤2cm	98 (66.67%)	30 (61.22%)
>2 cm	49 (33.33%)	19 (38.78%)

Compared to those who had no recurrence, those who had recurrence were more likely to have higher tumor stage (III) and a family history of cancer. No statistically significant difference was observed for age, ethnicity, education, cigarette smoking status, alcohol consumption status, tumor grade, and tumor size. In terms of AL, breast cancer patients who had recurrence had higher levels of AL at baseline than those who had no recurrence (Mean: 3.47 vs 2.55, P<0.001). We categorized the patient population into two groups based on AL, namely the low AL group (AL≤2) and the high AL group (AL>2). Then, we compared the distribution of selected characteristics by two AL groups. **(Table 3).**

Table 3: Sociodemographic, healthy behavioral, and clinical factors in controls by AL levels			
Variable	Low AL (≤2)	High AL (>2)	P value
Age category			
<55 years old	36 (48.00%)	30 (41.67%)	
≥ 55 years old	39 (52.00%)	42 (58.33%)	0.44
Ethnicity, n (%)			
Whites	57 (76.00%)	58 (80.56%)	
Blacks	8 (10.67%)	9 (12.50%)	
Hispanics	10 (13.33%)	5 (6.94%)	0.433
Education			
At least College graduate	22 (29.33)	18 (25.00%)	
Below college graduate	53 (70.67)	54 (75.00%)	0.555
Smoking status			
Never	60 (80.00%)	43 (59.72%)	
Former/current	15 (20.00%)	29 (40.28%)	0.007
Alcohol consumption			
Never	34 (45.33%)	40 (55.56%)	
Former/current	41 (54.67%)	32 (44.44%)	0.215
Family history of cancer			
No	36 (48.00%)	36 (50.00%)	
Yes	39 (52.00%)	36 (50.00%)	0.808
Tumor stage			
I/II	63 (84.00%)	54 (75.00%)	
III	12 (16.00%)	18 (25.00%)	0.176
Tumor grade			
Well/moderately differentiated	59 (78.67%)	51 (70.83%)	
poorly differentiated	16 (21.33%)	21 (29.17%)	0.274
Tumor size			
≤2cm	54 (72.00%)	44 (61.11%)	
>2 cm	21 (28.00%)	28 (38.89%)	0.161

The only statistically significant association was observed for cigarette smoking. We found that current and former smokers were more likely to be in the high AL group (P=0.007) than never smokers. Women with adverse tumor characteristics, including poorly differentiated tumors, high tumor grade (III), and large tumor size (>2cm) were more likely to be in the high AL group, though the P value didn't reach statistical significance. Next, we assessed the association between AL and the risk of recurrence (**Table 4**).

Table 4: Association between AL and breast cancer recurrence				
Variable	Controls (N)	Cases (N)	Unadjusted, OR (95%CI)	djusted, OR (95% CI)*
AL scores (Continuous)/ per one unit	147 (100%)	49 (100%)	1.19 (1.02, 3.41)	1.17 (1.01, 3.62)
AL scores (Categorical)				
Low (≤2)	75 (51.02)	16 (32.65%)		
High (>2)	72 (49.98)	33 (67.35%)	2.15 (1.04, 4.55)	1.62 (1.02, 5.36)

As a continuous variable, one unit increase of AL was associated with a 1.19-fold increased risk of breast cancer recurrence in the univariate analysis (OR=1.19, 95%CI: 1.02, 3.41). After the adjustment of the family history of cancer, tumor stage, and grade, a significant association remained (OR=1.17, 95%CI: 1.01, 3.62). In further analysis, we categorized the patient population into two groups based on AL, namely the low AL group (AL≤) and the high AL group (AL>2). Compared to those in the low AL group, those in the AL group had a 1.96-fold increased risk of breast cancer recurrence in the univariate analysis (OR=2.15, 95%CI: 1.04, 4.55) and a 1.62-fold increased risk of breast cancer recurrence in the multivariate analysis (OR=1.62, 95%CI: 1.02, 5.36).

Discussion

To our knowledge, this is the first study to assess the role of AL at baseline in breast cancer recurrence. In the study, we found that ER+ and HER2- breast cancer patients who relapsed had significantly higher levels of AL at baseline than those who had no recurrence. In the risk assessment, one AL unit increase was associated with 17% increased risk of recurrence (OR=1.17, 95%CI: 1.01, 3.62). The results are consistent with the assumption that AL plays an important role in the whole spectrum of breast carcinogenesis. For example, two studies have reported that higher AL was associated with an increased risk of breast cancer[11, 12]. There are also several studies to show higher AL is associated with poorly differentiated breast tumors and other aggressive tumor characteristics[13, 14]. In addition, in a recent study, elevated AL was linked to all-cause mortality among breast cancer patients [16]. Thus, our findings add another piece of evidence to support the role of AL in breast carcinogenesis. Our findings are not surprising. As a biomarker of chronic stress, higher AL indicates an elevated exposure to chronic stress, which may mechanistically lead to the disruption of stress response and consequently lead to impaired endocrine and immune function, accumulation of somatic mutations, inhibited repair of damaged DNA, and stress-induced adverse behaviors[10, 20, 21]. Eventually, it results in a higher likelihood of recurrence among breast cancer patients. Interestingly, after the adjustment of sociodemographic, healthy behavioral, and clinical factors, the significant association between AL and breast cancer recurrence remained. Though AL can be affected by sociodemographic, healthy behavioral, and clinical factors, our findings still suggest that the risk association between AL and breast cancer recurrence is independent of those known contributing factors. Thus, it would be interesting to include AL as an independent risk factor in the existing breast cancer recurrence risk prediction models and assess its utility in recurrence risk prediction. In addition, given the availability of both pharmacologic and non-pharmacologic stress reduction strategies[22, 23], it would be worthwhile to assess whether those strategies may reduce AL and ultimately improve clinical outcomes among breast cancer patients. There is no golden standard on how to construct an AL score [24-26]. In this study, we employed the sum of at-risk clinical scores, calculating AL based on set clinical definitions of “healthy” and “unhealthy” lab or clinical values. In sensitivity analysis, we further measured AL using the tertile method, which is also commonly used in AL calculation. In this method, the risk is defined based on the tertile distribution of each biomarker, except a history of medication to control metabolic disease and hypertension. Individuals in the lowest tertile (most healthy) will be assigned as 0, middle tertile as 1, and highest tertile (most unhealthy) as 2. Then, points will be summed to obtain a continuous measure for the AL score (**Supplement Table 2**). We found that the significant association between AL and breast cancer recurrence remained (**Supplement Table 3**). The consistency suggests the results were not subject to the difference in AL calculation methods. The major strength of this study is the nested case-control study design. The main weakness of this study is the relatively small sample size, which limits our ability to explore whether the association between AL and breast cancer recurrence differs by demographic, healthy behavioral, and clinical characteristics. Due to insufficient data on employment (~42%) and income (~65%), we only assessed education as a SES-related variable in this study. However, as shown previously, education, employment, and income are highly correlated[27]. Also, we do not have the statistical power to consider neighborhood influence on the association. In addition, the latent tumor may cause physiologic disruptions that influence biomarker levels for the AL markers. Unfortunately, we don’t have macheted tumor tissue in this study. So, the effect from tumors cannot be assessed.

Furthermore, we do not have the Oncotype Score for the study participants. Finally, in this study, we matched the cases and controls on two factors: time since diagnosis and chemotherapy status, using cumulative density sampling. Matching on two factors may reduce the number of eligible controls and potentially lead to the reduced representativeness of the population at risk. It may also reduce the generalizability of the study.

Conclusion

This is the first study to interrogate the relationship between AL at the time of disease diagnosis and the risk of recurrence among ER+HER2- breast cancer patients. Due to small sample size, the results are only preliminary and need to be further validated in future large studies.

Authors’ contributions

JS, YY, WHC, and HZ helped in conceptualization; JS, YY, and HZ helped in methodology; JS and HZ worked in software; YY helped in formal analysis; JS and HZ helped in data curation; JS, YY, and HZ contributed to writing—original draft preparation; all contributed to writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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