JACC: CARDIOONCOLOGY VOL. 6, NO. 5, 2024

ORIGINAL RESEARCH

Life's Essential 8 and Incident Cardiovascular Disease in U.S. Women With Breast Cancer

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ABSTRACT

BACKGROUND Relationships between lifestyle risk factors and cardiovascular disease (CVD) risk in women with breast cancer (BC) are underexplored.

OBJECTIVES To evaluate the incidence of CVD in relation to the Life's Essential 8 (LE8) score among women with BC.

METHODS Data from the Women's Health Initiative were utilized. The primary exposure was the LE8 score assessed prior to BC diagnosis. The LE8 score was stratified into low (0-59), moderate (60-79), and high (80-100) cardiovascular health (CVH). The primary endpoint was a composite of incident CVD events, which included coronary heart disease, defined as myocardial infarction along with coronary revascularization, CVD death, and stroke. We calculated the cumulative incidence of CVD and estimated hazard ratios.

RESULTS Among 7,165 participants, the median age was 70.1 years at BC diagnosis. The mean LE8 score was 62.0 ± 12.2. Over a median follow-up period of 6 years, 490 composite CVD events occurred. The risk of CVD events was highest for low CVH compared with moderate and high CVH. Compared with low CVH, the hazard ratio for incident CVD was 0.57 (95% CI: 0.46-0.69) for moderate CVH and 0.34 (95% CI: 0.20-0.59) for high CVH. LE8, in conjunction with age, provided a C-statistic of 0.74 for the composite risk of CVD.

CONCLUSIONS Higher LE8 scores were associated with a lower risk of incident CVD among women with BC in the United States. (JACC CardioOncol 2024;6:746-757) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 27, 2024; revised manuscript received July 10, 2024, accepted July 12, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.07.008

An estimated 4 million women in the United States are living with invasive breast cancer (BC), two-thirds of whom (>2.7 million) are over the age of 65 years.[1] Advances in BC-related screening and treatment have resulted in improved survival, and 90.8% of women with BC are expected to survive at least 5 years after initial diagnosis.[2] However, among postmenopausal women living with BC, cardiovascular disease (CVD) remains a leading cause of morbidity and mortality.[3] Compared with women without BC, researchers have observed that women with BC have a 1.8 times higher risk of death from CVD.[4] The increased burden of CVD in women with BC is thought to be multifactorial in etiology, including exposure to chemotherapy, radiation therapy, and pre-existing modifiable lifestyle risk factors, such as excess body weight, physical inactivity, and alcohol intake.[5-7] Despite this, there are no validated tools to identify women with BC who are at greatest risk of developing CVD after cancer.

In 2022, the American Heart Association (AHA) created the Life's Essential 8 (LE8) score, a tool to characterize ideal cardiovascular health (CVH), which encompasses positive health behaviors alongside traditional modifiable risk factors. LE8 includes key metrics including diet, physical activity, avoidance of nicotine, sleep, weight, lipid levels, blood glucose, and blood pressure.[7] LE8 expanded upon Life's Simple 7 (LS7) with an updated scoring system and the addition of sleep health as the eighth component to measuring CVH. In the general population, the LS7 and LE8 scores have demonstrated a strong ability to identify high-risk groups for several cardiovascular outcomes.[9] In a Women's Health Initiative (WHI) study of 161,808 participants, women with the lowest (worst) LS7 CVH scores had nearly 6.83 times the risk of incident CVD, defined as myocardial infarction, stroke, coronary bypass surgery, percutaneous transluminal coronary angioplasty, angina, or CVD-related death, compared with women with the highest (best) scores.[8] A study of nearly 20,000 adults demonstrated those with low CVH based on the LE8 score had a 1.61 and 3.13 times higher risk of all-cause and CVD-specific mortality, respectively.[9] However, no data are available on the clinical utility of using the LE8 score for risk stratification in women who are subsequently diagnosed with BC. Because women with BC are exposed to cardiotoxic treatment regimens, which alters the downstream risk for incident CVD, a knowledge gap persists regarding the applicability of tools developed for the general population, such as LE8, to the BC cohort.

Early CVD risk assessment upon BC diagnosis is critical, as better CVH prior to cancer diagnosis has been associated with decreased incidence of subsequent CVD development.[10] For women with a recent diagnosis of BC, a CVD risk assessment of modifiable lifestyle risk factors, such as the LE8 score, may serve as a tool to stratify and target high-risk groups at BC diagnosis, facilitating timely CVD risk reduction interventions. This study aimed to investigate the association of precancer LE8 with incident CVD in women with BC.

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association
BC = breast cancer
CHD = coronary heart disease
CVD = cardiovascular disease
CVH = cardiovascular health
LE8 = Life's Essential 8
LS7 = Life's Simple 7
MI = myocardial infarction
SEER = Surveillance Epidemiology and End Results
sHR = subdistribution hazard ratio
WHI = Women's Health Initiative

METHODS

PARTICIPANTS. The WHI is a national, prospective cohort study of postmenopausal women. The WHI study enrolled a total of 161,808 postmenopausal women 50 to 79 years of age at 40 clinical centers from 1993 to 1998 in the United States.[11] Participants were enrolled in either an observational study or 1 of 3 clinical trials. Participants were initially followed through March 2005 and had the option to continue follow-up in subsequent extension studies through 2020 (extension study 1 [2005-2010] and extension study 2 [2010-2020]).[12] Participants provided written informed consent at beginning of enrollment and at beginning of each extension study. The institutional review boards from all WHI-affiliated institutions approved this study.

The present study included participants in the observational study and clinical trial cohorts who were diagnosed with incident, invasive (stage I-III) BC during WHI follow-up through extension study 2 (n = 8,243). Participant reports of BC were verified by centrally trained adjudicators.[12] Clinical information about BC diagnosis and characteristics included staging (using Surveillance Epidemiology and End Results [SEER] classification, which incorporated tumor size and lymph node status), estrogen receptor, progesterone receptor, HER2 expression, and pathology review using SEER criteria). The sample was further restricted to remove participants who were diagnosed with CVD (coronary heart disease [CHD]/myocardial infarction [MI] and stroke) prior to their BC diagnosis and those missing 1 or more LE8 metrics, resulting in a final sample size of 7,165 participants for our analytic cohort (Supplemental Figure 1).

CVH METRICS. The 8 CVH metric scoring and frequency of data collection in the WHI are detailed in Supplemental Table 1.[7] In summary, diet was measured using the 2015 Healthy Eating Index score calculated from self-reported food frequency questionnaires. Percentile scores were based on population data from the National Health and Nutrition

Examination Survey.[13] Physical activity was measured as self-reported minutes of moderate or vigorous activity per week. Body mass index and blood pressure were measured during in-person at clinic visits. Sleep health was self-reported as the average number of hours of sleep per night. Nicotine exposure scoring was modified from the original AHA scoring given the constraints of the WHI data. Nicotine exposure was similarly defined based on self-report questionnaires and categorized as never, previous, or current smoker in a prior study.[9] Blood lipids and blood glucose were measured in blood samples during the WHI study visits. For participants that self-reported taking lipid-lowering medications on questionnaire data, the blood lipid score was reduced by 20 points.[7] Last, given that glycosylated hemoglobin was unavailable on the majority of participants in the WHI, the blood glucose score was modified using data on fasting blood glucose and treatment for diabetes similar to a previously published study.[8] Participants with insulin-treated diabetes were given 0 points. Participants with diabetes on oral medication were given 20 points, and participants with diet-treated diabetes were given 40 points. On the other hand, participants without diabetes and fasting blood glucose ranging from 100 to 125 mg/dL were assigned 60 points, and participants without diabetes and fasting blood glucose <100 mg/dL were assigned 100 points. Each metric has a total possible score of 100, and the unweighted subscores were added and divided by 8 for a final LE8 score that ranged from 0 to 100, with higher scores indicating a more favorable health state. Given the high degree of missing data for the lipid metric score (n = 5,525), our primary analysis excluded the lipid metric from the LE8 total score (scores were added and divided by 7). The final score was categorized into low (0-49 points), moderate (50-79 points), and high (80-100 points) CVH status based on AHA-defined categories.[7] The primary exposure was the LE8 score, which was calculated using data from the most recent assessments of LE8 metrics but prior to BC.

OUTCOME. The primary outcome was the composite of incident CVD, which included CHD, CVD death, and stroke. Methods for ascertaining and classifying outcomes for CVD have been published previously.[12] CHD was defined as an acute MI requiring hospitalization along with coronary revascularization procedures such as coronary artery bypass or percutaneous transluminal coronary angioplasty. Both definite and probable MIs were included and were classified using an algorithm that consisted of a combination of medical history, electrocardiogram readings, and cardiac biomarkers.

CVD death included all deaths associated with definite or possible CHD, deaths associated with stroke or pulmonary embolism, heart failure, and other CVD deaths not related to CHD. CHD deaths specifically were defined as death with an underlying cause of CHD with 1 or more of the following: hospitalization for MI within 28 days before death, death resulting from a procedure related to coronary artery disease, or a death certificate indicating CHD as the underlying cause of death.

Stroke was included as outcomes if hospitalization was required. Stroke was defined as having a rapid onset of persistent neurologic deficit attributed to an obstruction or rupture of the brain arterial system without evidence for other cause and supported by imaging studies.

Potential outcomes were identified through semiannual or annual medical update questionnaires. Medical records for all self-reported events were reviewed by central physician adjudicators (for CHD death) or trained local adjudicators (for all other cardiovascular end points) using standardized criteria.

COVARIATES. Sociodemographic variables included age at BC diagnosis, race, ethnicity, income, education, cancer stage (ie, stage, grade), alcohol consumption (servings/week), waist circumference (cm), prevalent hypertension, prevalent heart failure, and use of cardiac medications (ie, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, calcium channel blockers, statins). Race, ethnicity, income, and education were ascertained from self-report questionnaires at WHI enrollment. Cancer stage (localized [SEER stage 1/2] vs regional [SEER stage 3]), grade, and age at BC diagnosis were ascertained through adjudication procedures at the time of BC diagnosis. Waist circumference was collected at clinic visits on all participants at baseline and year 3 as well as yearly in the clinical trial participants. History of hypertension and heart failure were obtained through self-report medical history questionnaires updated yearly. Cardiac medication data were obtained through medical inventory questionnaires completed by all participants at WHI enrollment and at year 3, as well as at years 1, 6, and 9 in the clinical trial participants. For all variables measured at multiple timepoints, the timepoint closest to but prior to BC diagnosis was

used. Additionally, all models included the WHI study component (clinical trial vs observational study) as a covariate.

STATISTICAL ANALYSIS. Participant characteristics of the overall sample were obtained and reported using mean ± SD, median (Q1-Q3), or frequency and proportion for continuous and categorical variables. Bivariate statistics employed *t* tests and chi-square tests for continuous and categorical variables, respectively, to compare categories of LE8 based on AHA-defined categories (0-49 low, 50-79 moderate, and 80-100 high). To evaluate changes over time in LE8 scores prior to BC, we calculated the frequencies of participants who transitioned LE8 categories between WHI enrollment and most recent assessment prior to BC and visualized these changes using a Sankey diagram.

To evaluate the cumulative incidence of CVD with LE8 in women with BC, the analysis used time-to-event methods. Follow-up time started at BC diagnosis, and participants were followed until first of incident CVD event, non-CVD death, or time of last follow-up, whichever came first. Cumulative incidence curves, accounting for the competing risk of non-CVD death, were generated for each LE8 category. The difference in cumulative incidence by LE8 categories was tested using Gray's test. We used Fine and Gray subdistribution hazards models to estimate the risk of LE8 based on development of CVD in stepwise models. Subdistribution hazard ratios (sHRs) and 95% CIs were calculated. Model 1 was adjusted for age at BC diagnosis and model 2 included age at BC diagnosis and cancer stage. LE8 was modeled both as a continuous variable (per 10 points) and as a categorical variable (low CVH as reference). The linearity assumption was checked using goodness-of-fit testing based on the cumulative sums of residuals for Fine and Gray models.[14]

We conducted exploratory analyses to determine if: 1) CVD was associated with any individual LE8 subscores; or 2) any individual CVD outcome was associated with LE8 total score. For these exploratory analyses, we used a Bonferroni correction to account for multiple testing equal to 0.05 divided by the number of tests. We also accounted for the competing risk of all-cause death in separate Fine and Gray models to calculate the sHRs. We additionally explored whether the association between precancer LE8 with incident CVD in women with BC differed compared with a matched cohort of cancer-free women. This exploratory analysis was done in a subset of women with BC who were enrolled in the LILAC (Life and Longevity After Cancer) study, a cancer survivorship sub cohort in the WHI (n = 4,365). The LILAC data were utilized in this analysis, as the LILAC study previously developed a matched cohort of cancer-free control individuals with index dates calculated to coincide with BC diagnosis dates in the BC cohort, ensuring comparable follow-up periods and a standardized starting point for time-to-event analysis. Per LILAC protocols, to be included in the cancer-free matched cohort, LILAC participants had to be free of cancer through death or end of follow-up in 2020. Each BC participant was matched to no more than 5 cancer-free control individuals, resulting in a cohort of 20,995 cancer-free control individuals. We performed a Fine and Gray subdistribution hazard model to test the difference in the association of LE8 score with incident CVD in the BC cohort vs the cancer-free cohort by including an interaction term between the LE8 score*BC case status (cancer vs cancer-free). Follow-up time started at BC diagnosis in the BC cohort or a similar index date in the cancer-free cohort. We conducted several sensitivity analyses: 1) we explored whether the addition of cancer treatments to the model improved risk discrimination in a subset of women with treatment data available (n = 3,404); 2) we explored whether inclusion of the lipid metric in the final LE8 modified the results in a sample of participants who had data for all 8 LE8 metrics (n = 1,169); 3) we explored whether the associations changed after excluding women with heart failure prior to BC (n = 145); and 4) we explored whether the associations differed according to cancer stage (localized vs regional) or average time between the LE8 metrics and BC diagnosis. For this analysis, we calculated the average time (in years) between all of the LE8 metrics (excluding the lipid metric) and BC for each person. This was then categorized as between 0 and ≤1 years, between 1 and ≤3 years, and >3 years.

Statistical analyses were performed using R Version 4.2.3 (R Foundation for Statistical Computing) and a *P* value ≤0.05 indicates statistical significance in the main analyses.

RESULTS

BASELINE CHARACTERISTICS. Baseline characteristics of study participants are presented in **Table 1**. A total of 7,165 participants with BC were included in the present study. The mean age at diagnosis of BC was 70.1 ± 7.5 years. The mean CVH score was 62.0 ± 12.2. At baseline, 16.3%, 77.1%, and 6.6% had low, moderate, and high CVH scores, respectively. Overall, 89.2% were White/Caucasian participants, 6.3% were Black/African American participants, and 4.5% were Asian, American Indian, or Hispanic/Latino

TABLE 1 Baseline Characteristics of Study Participants: Overall and by LE8 Categories

	Overall (N = 7,165)	Low (0-49) (n = 1,169)	Intermediate (50-79) (n = 5,525)	High (80-100) (n = 471)	*P* Value
Demographics					
Age at diagnosis, y	70.1 ± 7.5)	69.8 ± 7.3	70.3 ± 7.5	68.4 ± 7.7	<0.001
Education					<0.001
<HS	240 (3.4)	100 (8.6)	135 (2.4)	6 (1.3)	
HS or GED	1,038 (14.6)	233 (20.1)	787 (14.2)	27 (5.8)	
>HS-bachelor's	3,499 (49.2)	612 (52.7)	2,709 (49.0)	201 (42.9)	
>Bachelor's	2,338 (32.9)	217 (18.7)	1,897 (34.3)	234 (50.0)	
Income					<0.001
<$34,999	2,411 (35.0)	580 (51.7)	1,768 (33.0)	79 (17.8)	
$35,000-$74,999	2,899 (42.1)	383 (34.1)	2,336 (43.6)	193 (43.4)	
$75,000-$99,999	659 (9.6)	71 (6.3)	535 (10.0)	60 (13.5)	
>$100,000	751 (10.9)	56 (5.0)	595 (11.1)	104 (23.4)	
Race					<0.001
Black	451 (6.3)	186 (15.9)	257 (4.7)	8 (1.7)	
White	6,394 (89.2)	917 (78.4)	5,031 (91.1)	446 (94.7)	
Other reported	320 (4.5)	65 (5.7)	237 (4.3)	17 (3.6)	
WHI clinical trial	2,929 (40.9)	592 (50.6)	2,207 (40.0)	130 (27.6)	<0.001
Cancer characteristics					
Stage					0.050
Localized	5,484 (76.5)	864 (73.9)	4,264 (77.2)	356 (75.6)	
Regional	1,681 (23.5)	305 (26.1)	1,261 (22.8)	115 (24.4)	0.029
Grading					
Well differentiated	1,844 (25.7)	250 (21.4)	1,472 (26.6)	122 (25.9)	
Moderately differentiated	2,904 (40.5)	487 (41.7)	2,228 (40.3)	189 (40.1)	
Poorly differentiated	1,639 (22.9)	301 (25.7)	1,232 (22.3)	107 (22.7)	
Anaplastic	159 (2.2)	25 (2.1)	126 (2.3)	8 (1.7)	
Unknown	619 (8.6)	107 (9.2)	467 (8.5)	45 (9.6)	
Cancer treatment[a]					
Chemotherapy	1,051 (30.9)	143 (32.5)	826 (30.6)	82 (30.5)	0.73
Radiation	2,386 (70.1)	302 (68.6)	1,898 (70.4)	186 (69.1)	0.86
Endocrine therapy	2,329 (68.4)	305 (69.3)	1,838 (68.2)	186 (69.1)	0.73
Clinical characteristics					
BMI, kg/m^2	28.4 ± 6.0	34.0 ± 6.5	27.6 ± 5.3	23.3 ± 2.5	<0.001
Systolic BP, mm Hg	126.2 ± 17.2	134.8 ± 16.8	125.5 ± 16.7	112.6 ± 12.2	<0.001
Diastolic BP, mm Hg	73.2 ± 9.4	75.7 ± 10.0	73.1 ± 9.2	68.0 ± 7.2	<0.001
Smoking history					<0.001
Never	3,524 (49.2)	333 (28.5)	2,774 (50.2)	417 (88.5)	
Former	3,184 (44.4)	621 (53.1)	2,509 (45.4)	54 (11.5)	
Current	457 (6.4)	215 (18.4)	242 (4.4)	0 (0.0)	
Alcohol use, servings/wk	2.0 ± 4.1	1.4 ± 3.8	2.1 ± 4.2	2.1 ± 4.0	<0.001
Physical activity, MET/min/wk	100.6 ± 138.0	13.8 ± 54.8	107.0 ± 137.0	240.7 ± 152.7	<0.001
HEI 2015	67.2 ± 10.2	58.6 ± 10.1	68.3 ± 9.3	75.4 ± 6.4	<0.001
Comorbidities					
Hypertension	3,436 (48.0)	799 (68.4)	2,536 (45.9)	101 (21.4)	<0.001
Diabetes	623 (8.7)	385 (32.9)	238 (4.3)	0 (0.0)	<0.001
HF	145 (2.0)	53 (4.5)	92 (1.7)	0 (0.0)	<0.001

Continued on the next page

participants. Localized BC at diagnosis was found in 76.5% of participants. Lower CVH was more common among minorities, older participants, and participants with lower educational attainment. The distributions of the LE8 component scores by LE8 categories are presented in Supplemental Table 2. Participants with missing lipid metric scores had a higher percentage of Black women, higher mean physical activity, and lower percentage of hypertension, diabetes, and congestive heart failure, but the mean CVH did not differ substantially from those with complete LE8 data (Supplemental Table 3). Supplemental Table 4 reports the median time between the assessment of each individual LE8 metric

TABLE 1 Continued

	Overall (N = 7,165)	Low (0-49) (n = 1,169)	Intermediate (50-79) (n = 5,525)	High (80-100) (n = 471)	*P* Value
Medications					
Beta-blockers	824 (11.5)	179 (15.4)	616 (11.1)	29 (6.2)	<0.001
Calcium-channel blockers	771 (10.9)	212 (18.0)	541 (9.8)	18 (3.8)	<0.001
ACE inhibitor	676 (9.3)	198 (17.1)	452 (8.2)	15 (3.2)	<0.001
ARB	204 (2.8)	61 (5.2)	141 (2.5)	2 (0.4)	<0.001
Diuretic	1,214 (16.9)	301 (25.9)	886 (16.1)	27 (5.7)	<0.001
Statin	1,105 (15.4)	285 (24.6)	799 (14.5)	21 (4.5)	<0.001
Laboratory values					
Total cholesterol, mg/dL	227.0 ± 40.4	227.6 ± 43.8	227.4 ± 39.6	219.9 ± 35.0	0.33
HDL, mg/dL	55.1 ± 15.2	51.1 ± 13.3	56.1 ± 15.6	62.4 ± 13.4	<0.001
Non-HDL, mg/dL	172.4 ± 42.2	176.1 ± 43.2	172.2 ± 42.1	154.8 ± 33.8	0.002
Fasting glucose, mg/dL	101.3 ± 29.3	119.9 ± 45.7	95.6 ± 17.3	86.6 ± 11.2	<0.001
LE8 score	62.0 ± 12.2	42.2 ± 5.6	64.4 ± 7.7	82.8 ± 2.3	<0.001

Values are mean ± SD or n (%). Baseline refers to the time point of variable assessment closest but prior to BC for each participant. [a]Only a subset of the WHI sample have cancer treatment data available in this cohort (n = 3,404 [48%]) as cancer treatments were only abstracted in a subcohort within the WHI.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; HEI = healthy eating index; HF = heart failure; HS = high school; LE8 = Life's Essential 8; MET = metabolic equivalent of task; WHI = Women's Health Initiative.

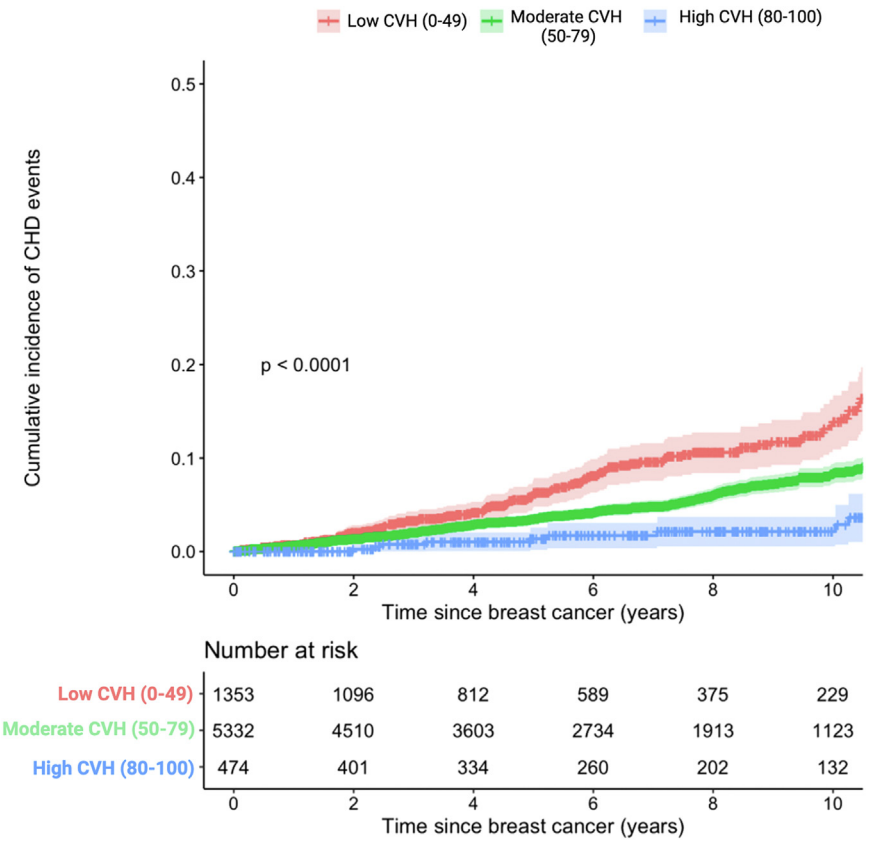
and BC diagnosis. The majority of women had data available on LE8 metrics within 3 years prior to BC diagnosis. Physical activity data were available within 0.9 years of diagnosis. Most participants remained in the same LE8 category between WHI enrollment and the most recent assessment pre-BC. In total, 13% of participants changed categories, with 4% changing from intermediate to low, 4% changing from low to intermediate, 2% changing from high to intermediate, and 2% changing from intermediate to high CVH. No participants changed from high to low or low to high CVH (Supplemental Figure 2).

INCIDENCE OF CVD BY LE8. During a median follow-up period of 6.0 years (Q1-Q3: 3.0-9.3 years), a total of 490 composite CVD events occurred. Of the 490 composite outcomes, 245 events were due to CHD/MI, 219 were due to stroke, and 26 were due to other CVD death. Additionally, there were 2,630 non-CVD death competing events. Compared with individuals with low CVH, those with moderate and high CVH had a lower incidence of CVD (Gray's test $P < 0.001$) (**Figure 1**). The cumulative incidence at 10 years for CVD was 16.2%, 9.1%, and 1.5% for low, moderate, and high CVH, respectively.

ASSOCIATION BETWEEN LE8 AND INCIDENT CVD. In the fully adjusted model, compared with those with a low CVH, those with moderate CVH (sHR: 0.57; 95% CI: 0.46-0.69) and high CVH (sHR: 0.34; 95% CI: 0.20-0.59) had a significantly lower risk of CVD (**Table 2**). As a continuous variable, a 10-point difference in LE8 scores was associated with a 21% lower risk of CVD (sHR: 0.79; 95% CI: 0.73-0.85) (**Table 2**). LE8, either as a categorical variable or as a continuous variable, provided a C-statistic of 0.74 for incident CVD when combined with age (**Table 2**). The addition of cancer stage or cancer treatments did not add much incremental discriminatory ability for the model (**Table 2**, Supplemental Table 5).

Examining the association between each of the LE8 components (excluding the lipid metric) revealed significant associations between nicotine exposure, blood glucose, and blood pressure with risk of CVD. Compared with the reference score of 100, the lowest CVH status in nicotine exposure was associated with a HR of 1.83 (95% CI: 1.33-2.53), a HR of 1.94 (95% CI: 1.20-3.15) for blood glucose, and a HR of 1.94 (95% CI: 1.09-3.48) for blood pressure (**Figure 2**). In contrast, diet, physical activity, and sleep were not significantly associated with incident CVD (**Figure 2**). When examining the association between LE8 and individual CVD outcomes, LE8 was significantly associated with only CHD/MI. Relative to the low-CVH group, the risk of CHD/MI was 55% (sHR: 0.45; 95% CI: 0.35-0.58) and 76% (sHR: 0.24; 95% CI: 0.11-0.53) lower for participants in the moderate and high-CVH group, respectively (**Table 3**). LE8 was not associated with stroke in these participants (**Table 3**). Results were similar when restricting the analysis to those with complete LE8 metrics, including the lipid metric (Supplemental Table 6). Additionally, our results did not differ according to cancer stage or average time between LE8 metrics and BC diagnosis (Supplemental Tables 7 and 8). Last, our results remained unchanged after

FIGURE 1 Cumulative Incidence of CVD Events per CVH Category



During a median follow-up period of 6.0 years (Q1-Q3: 3-9.3 years), a total of 490 composite cardiovascular disease (CVD) events occurred. Compared with individuals with low cardiovascular health (CVH), those with moderate and high CVH had a lower incidence of CVD (Gray's test $P < 0.001$). The cumulative incidence at 10 years for CVD was 16.2%, 9.1%, and 1.5% for low, moderate, and high CVH, respectively. CHD = coronary heart disease.

excluding women with pre-existing heart failure or incident heart failure prior to BC (Supplemental Table 9).

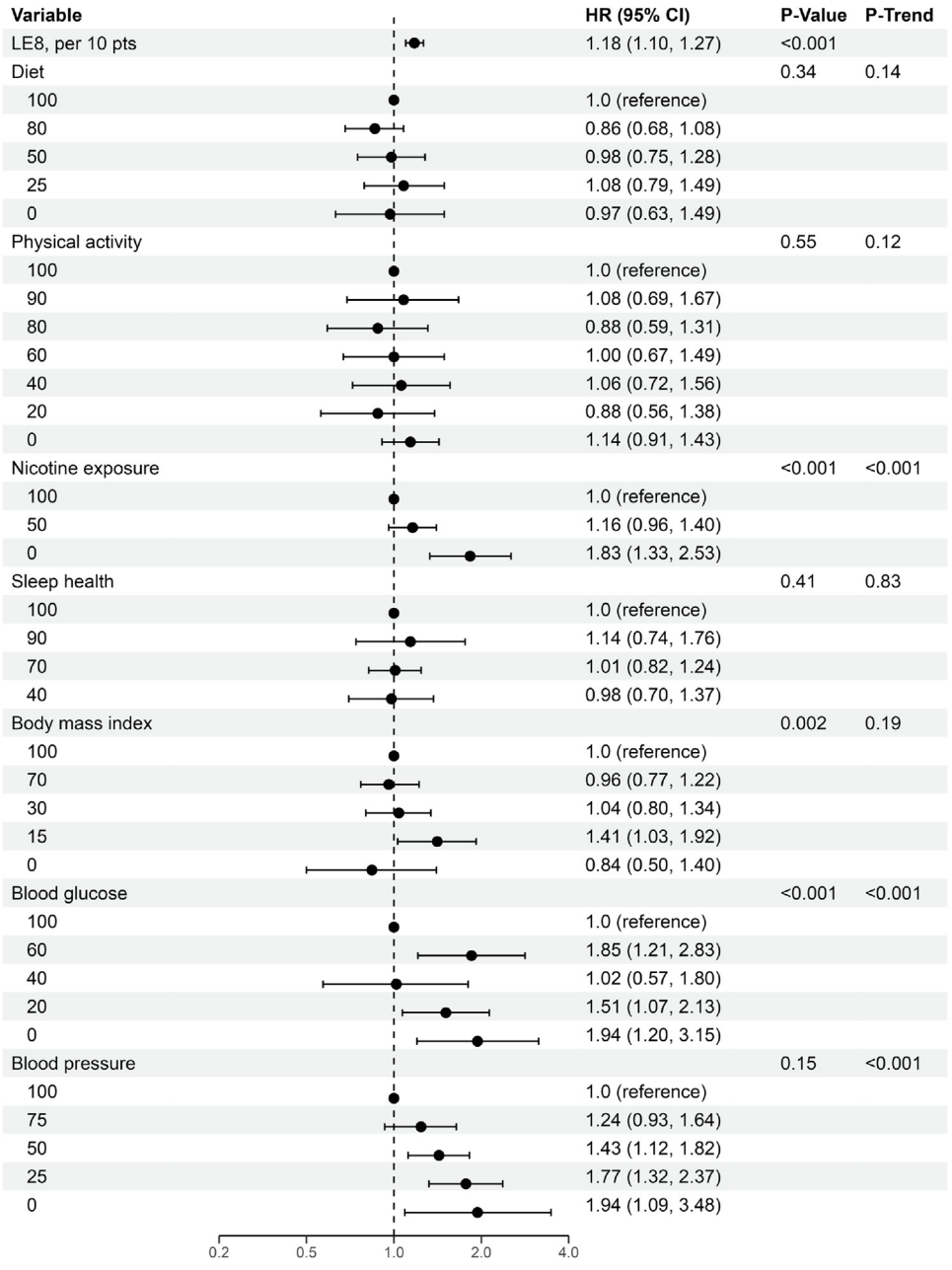
ANALYSIS OF COMPARISON WITH CANCER-FREE CONTROL SUBJECTS. Baseline characteristics were similar between BC cases from the LILAC cohort and their matched non-BC control individuals (Supplemental Table 10). With a median follow-up time of 5.2 years (Q1-Q3: 2.5-8.6 years), 329 and 1,593 CVD events occurred among cancer cases and control individuals, respectively. Results were consistent in those with and without cancer. In those

TABLE 2 Subdistribution Hazard Models Evaluating the Association of LE8 Score With Incident CVD (n = 490) Considering LE8 as Both Continuous and Categorical

	Model 0		Model 1		Model 2	
	sHR (95% CI)	C-Index (95% CI)	sHR (95% CI)	C-Index (95% CI)	sHR (95% CI)	C-Index (95% CI)
LE8, per 10 points	0.79 (0.74-0.85)	0.59 (0.56-0.62)	0.79 (0.73-0.85)	0.74 (0.71-0.76)	0.79 (0.73-0.85)	0.74 (0.71-0.76)
LE8, categorical		0.57 (0.54-0.60)		0.74 (0.71-0.76)		0.74 (0.71-0.76)
Low	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Moderate	0.59 (0.48-0.71)		0.57 (0.46-0.69)		0.57 (0.46-0.69)	
High	0.32 (0.19-0.54)		0.34 (0.20-0.59)		0.34 (0.20-0.59)	

Model 0: LE8 + WHI clinical trial; model 1: model 0 + age at diagnosis; model 2: model 1 + cancer stage. All associations were significant with $P < 0.001$.
sHR = subdistribution hazard ratio; other abbreviations as in Table 1.

FIGURE 2 **Individual Components of LE8 Components and Risk of CVD**



When examining the association between each of the Life's Essential 8 (LE8) components (excluding the lipid metric), nicotine exposure, blood glucose, and blood pressure were found to be significantly associated with risk of CVD. As compared with the reference score of 100, the lowest CVH status in nicotine exposure was associated with a HR of 1.83 (95% CI: 1.33-2.53), a HR of 1.94 (95% CI: 1.20-3.15) for blood glucose, and a HR of 1.94 (95% CI: 1.09-3.48) for blood pressure. In contrast, diet, physical activity, and sleep were not significantly associated with incident CVD. Abbreviations as in Figure 1.

without cancer, each 10-point difference in LE8 resulted in a sHR of 0.76 (95% CI: 0.73-0.79). The C-statistic for incident CVD was 0.73. In those with cancer, each 10-point increase in LE8 was associated with a sHR of 0.81 (95% CI: 0.73-0.90), and a C-statistic of 0.77. However, the association did not differ between those with and without cancer (P interaction = 0.22) (Supplemental Table 11).

TABLE 3 Subdistribution Hazard Models for LE8 Score Associations and Individual Outcomes Stratified by CHD/MI and Stroke Considering LE8 as Both Continuous and Categorical

	CHD/MI (n = 270)[a]		Stroke (n = 245)[a]	
	sHR (95% CI)	*P* Value	sHR (95% CI)	*P* Value
LE8, per 10 points	0.72 (0.65-0.80)	<0.001	0.90 (0.81-1.01)	0.057
LE8, categorical		<0.001		0.096
Low	1.0 (reference)			
Moderate	0.45 (0.35-0.58)	<0.001	0.76 (0.56-1.04)	0.088
High	0.24 (0.11-0.53)	<0.001	0.50 (0.27-1.00)	0.051

[a]Adjusted for WHI clinical trial and age at diagnosis.
CHD = coronary heart disease; MI = myocardial infarction; other abbreviations as in Tables 1 and 2.

DISCUSSION

Our study investigated the association between CVH, as measured by the LE8 score, and incident CVD in women with BC and found the following: 1) a higher LE8 score prior to BC diagnosis was significantly associated with lower risk of incident CVD in women with BC; 2) a combination of the LE8 score with age was highly predictive of incident CVD after BC diagnosis, with a C-index of 0.74; and 3) LE8 was predictive of incident CHD/MI but lacked accuracy in identifying individuals at increased risk for stroke.

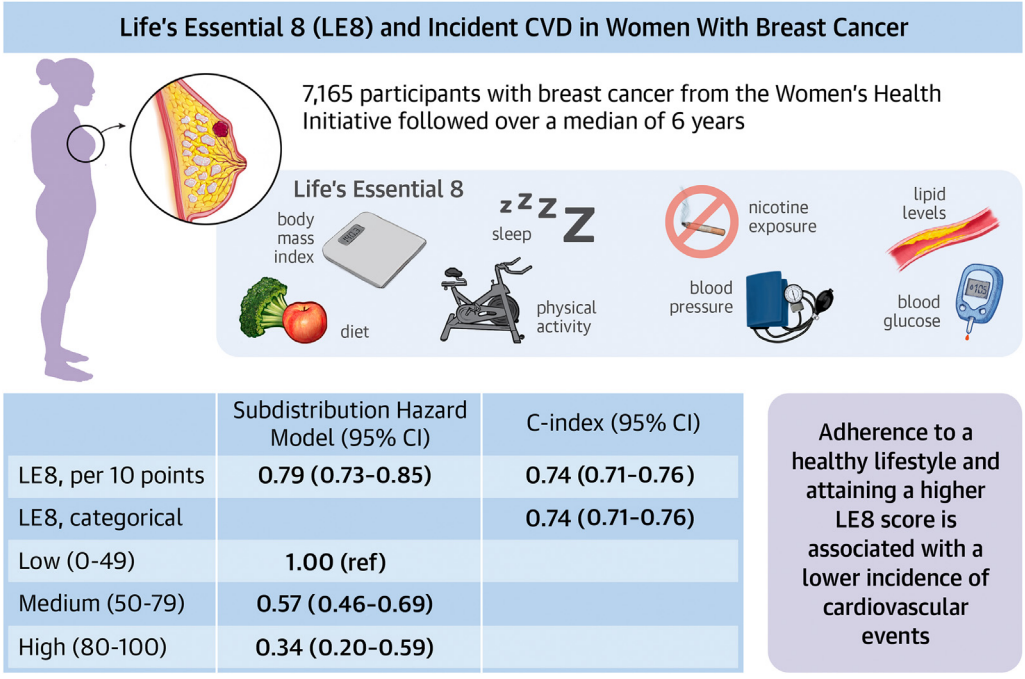
Women with BC face elevated risks for incident CVD events and CVD associated mortality compared with women without BC.[15] Given the high clinical and economic burden from downstream CVD morbidity and mortality in women with BC, there is an urgent need to better characterize which underlying lifestyle, clinical, socioeconomic, or cancer treatment exposures may be contributing to elevated CVD risk in this population.[4] Exposure to cardiotoxic BC treatment (including anthracyclines and radiation therapy) in the presence of traditional cardiovascular risk factors can potentiate an increase in risk for CVD.[5,6] Few studies have evaluated the role of lifestyle risk factors in women with BC. One study of 13,348 women with BC registered in the UK Biobank found that individuals with the healthiest lifestyle had an approximately 50% lower risk of incident CVD compared with those with the least healthy lifestyle.[16] The UK Biobank study evaluated a combination of lifestyle risk factors (including body mass index, tobacco use, alcohol use, dietary habits, and physical activity) and genetic predisposition to CVD with a polygenetic risk score. The lifestyle assessment was ascertained through standardized questionnaires at baseline. Similarly, in a study of 40,095 South Korean women with BC in the Korean National Health Insurance Service database, predicted high lean body and appendicular skeletal mass was associated with 32% lower CVD risk compared with those with low lean body mass.[17]

Our findings contribute to the limited body of evidence supporting the association between CVH and development of incident CVD in women with BC. To our knowledge, our study is the first to demonstrate a significant association between the LE8 model and incident CVD among women with BC in the United States (**Central Illustration**). This finding is unique in that all the domains within LE8 are modifiable (dietary health, physical activity level, nicotine use, sleep patterns, body mass index, blood pressure, blood glucose, and lipids). Cardio-oncology practices are well positioned to assess CVD risk prior to cancer treatment as a primary prevention strategy. Currently, guidelines recommend baseline cardiovascular risk assessment prior to starting cardiotoxic cancer treatment, but these factors are not systematically evaluated and there is no standardized approach to assessing lifestyle cardiovascular risk factors.[18] A standardized assessment of lifestyle risk factors using LE8 may potentially be used to stratify individuals into risk categories for future CVD. Most participants in our study fell under the moderate CVH range, which highlights a considerable opportunity for targeted efforts in optimizing CVH. Understanding which individuals are at increased risk for CVD may guide surveillance during and after cancer treatment.

There are emerging tools to identify women with BC who are at the highest risk of developing CVD after cancer. Prior models evaluating women with BC and their cardiovascular risk have been developed by incorporating an expansive combination of conventional and cancer treatment-related risk factors. A prediction model derived from a South Korean cohort included pre-existing CVD, baseline CVD risk factors (hypertension, age, body mass index, glomerular filtration rate, dyslipidemia, and diabetes), and cancer treatment exposures to predict major adverse cardiovascular events (including MI, heart failure, stroke/transient ischemic attack) after BC therapy with a C-index of 0.876.[19] Another prediction model was developed from women with BC in Ontario, Canada, using administrative databases, which included age and pre-existing comorbidities (including heart failure, atrial fibrillation, peripheral vascular disease, hypertension, ischemic heart disease, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and cerebrovascular disease) with a C-index of 0.819.[20]

Compared with the aforementioned risk models, LE8 consists of modifiable lifestyle factors that are obtained routinely. The LE8 model combined with

CENTRAL ILLUSTRATION **LE8 Score Predicts Incident CVD in Women with Breast Cancer**



	Subdistribution Hazard Model (95% CI)	C-index (95% CI)
LE8, per 10 points	0.79 (0.73-0.85)	0.74 (0.71-0.76)
LE8, categorical		0.74 (0.71-0.76)
Low (0-49)	1.00 (ref)	
Medium (50-79)	0.57 (0.46-0.69)	
High (80-100)	0.34 (0.20-0.59)	

Wadden E, et al. JACC CardioOncol. 2024;6(5):746-757.

Our study evaluated 7,165 postmenopausal women with breast cancer in the Women's Health Initiative (WHI). Compared with women with breast cancer with a low cardiovascular health (CVH), those with moderate CVH and high CVH had a significantly lower risk of cardiovascular disease (CVD). A 10-point difference in Life's Essential (LE8) scores was associated with a 21% lower risk of CVD. LE8, either as a categorical variable or as a continuous variable, provided a C-statistic of 0.74 for incident CVD when combined with age.

age (also easily obtainable) provided good discriminatory ability for incident MI/CHD/stroke with a C-statistic of 0.74. A strength of the LE8 score is the relative ease and availability of the clinical data points needed to calculate a score, making it a practical, easy-to-use instrument to implement in the cardio-oncology clinic. Of the stratified components of LE8, we found that BMI, nicotine exposure, blood glucose, and blood pressure were the modifiable risk factors most strongly associated with incident CVD. While individually diet, exercise, and sleep did not have associations with CVD risk, these cardiometabolic risk factors were self-reported and have been closely tied to overall CVD risk in the greater literature. In addition, stroke was not associated with the LE8 score; however, several plausible reasons may explain this finding. First, the performance of the LE8 may differ for each outcome and have resulted in a nonsignificant finding for stroke. Second, it is possible that our analyses were lacking in power based on the smaller sample size to detect associations with LE8 in stroke outcomes, given that a recent analysis of 32,896 U.S. adults found that each 10-point-higher overall LE8 score was associated with lower risk of 22% to 40% for CVD and 17% to 34% risk reduction for stroke.[21]

In the general population, many observational studies have investigated the role of improving lifestyle factors in reducing CVD risk,[22] and approximately 80% of CVD is thought to be preventable through healthy diet, physical activity, healthy weight, nicotine avoidance, controlling blood pressure, diabetes, and lipids.[23] Currently, no randomized trials have evaluated healthy lifestyle interventions in mitigating the risk for CVD in women with BC. A small cross-sectional study evaluated the impact of hypothetical cardiovascular risk factor optimization on the predicted 10-year risk of CVD (including MI, coronary revascularization, angina, stroke/transient ischemic attack) events using the Joint British Society cardiovascular risk calculator in women with BC receiving adjuvant therapy. Based on hypothetical cessation of smoking and improved blood pressure and cholesterol to normal levels, the optimization

model demonstrated a reduced 10-year predicted risk of CVD from 26.5% to 9.9% ($P = 0.005$) in the high CVD risk group.[24] Our findings suggest that interventions aimed at lifestyle modification in women with BC may potentially reduce downstream risk for incident CVD.

STUDY IMPLICATIONS. The findings of the present study suggest that LE8 may be an effective risk factor assessment tool for CVD in women with BC. Prior studies show that LE8 can be an informative tool to assess subsequent CVD risk in the general population.[25,26] Our results reinforce these findings and extend them to the BC cohort. Future intervention studies should be targeted at these modifiable risk factors to determine if an intervention program may result in significant reductions in incident CVD in women with BC.

STUDY LIMITATIONS. First, as an observational study, despite adjustments for potential confounders, residual confounding cannot be ruled out completely. Second, lifestyle factors were not measured at the time of BC diagnosis itself, and there was variability between the time of assessment and BC diagnosis. Changes in behavioral factors between the time of assessment and BC diagnosis may affect risk estimates. More frequent measurements may provide additional information. Third, many of the lifestyle factors were self-reported. Fourth, the original definition of LE8 included lipid levels as a metric. Unfortunately, only a subset of the cohort had complete data available, including lipid levels. However, a sensitivity analysis showed that the results between those with lipid values and those without lipid values were consistent. Fifth, the study mainly consisted of White participants; therefore, findings may not generalize to other racial groups. Sixth, given that our dataset lacked the ability to examine specific cancer treatments (anthracyclines, trastuzumab, etc.), future studies should incorporate the impact of specific cardiotoxic cancer treatments into their analyses. Additional studies including prospective studies or randomized clinical trials are needed to further identify optimal prevention strategies to prevent CVD events in women with BC.

CONCLUSIONS

Higher CVH and higher LE8 scores were significantly associated with lower risk of CVD risk among women with BC. Our results confirm the clinical significance of modifiable risk factors in CVD development in women with BC, particularly in the first several years after BC diagnosis. These findings suggest that, for women with BC, adopting a lifestyle with higher CVH and attaining a higher LE8 score may be a potential strategy to reduce the risk of CVD.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The WHI program is funded by National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. This manuscript was partially funded by a grant from Alpha Phi. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In postmenopausal women with BC, lifestyle risk factors as scored through the AHA's LE8 score measured prior to BC diagnosis were found to have strong associations with incident CVD after BC diagnosis, suggesting that modifiable lifestyle risk factors are strongly associated with CVD outcomes in this population.

TRANSLATIONAL OUTLOOK: Future studies are needed to further validate and understand the basis for these associations between lifestyle risk factors and development of CVD in individuals with BC and whether intervening on these risk factors may mitigate the risk for CVD.

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KEY WORDS behavioral risk factors, breast cancer, ischemic disease, lifestyle risk factors, women's oncology

APPENDIX For supplemental tables and figures, please see the online version of this paper.