The Associations Of Healthy Lifestyle Index With Breast Cancer Incidence And Mortality In A Population-Based Study

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Abstract

Purpose: To investigate how a healthy lifestyle index (HLI) is associated with breast cancer risk and survival in a population-based breast cancer study.

Methods: The study included 1,319 breast cancer cases and 1,310 controls from the population-based Long Island Breast Cancer Study Project, and its follow-up study of mortality. We determined vital status using the National Death Index (521 deaths, 210 from breast cancer; median follow-up 214.5 months). A healthy lifestyle index (HLI) score, was generated from information on body fatness, physical activity, intake of plant and animal foods, alcohol consumption, breastfeeding and smoking, with higher values representing engagement in healthier behaviors. Multivariable logistic and Cox regression were used to estimate breast cancer odds ratios (ORs) mortality hazards ratios (HRs), respectively.

Results: Compared to women in the low HLI tertile, women in the intermediate (OR=0.78, 95%CI=0.65-0.94) and high (OR=0.68, 95%CI=0.56-0.83) tertiles had a decreased odds of breast cancer, and a one-point increase in HLI score was associated a reduction in breast cancer risk (OR=0.85, 95%CI=0.79–0.92). Women in the intermediate (HR=0.75, 95%CI=0.61-0.91) and high (HR=0.74, 95%CI=0.60-0.92) tertiles had a decreased rate of all-cause mortality, and a one-point increase in HLI score was associated with a reduction in all-cause mortality (HR=0.83, 95%CI =0.76-0.91). These associations were significant among postmenopausal.

Conclusion: A healthy lifestyle may be beneficial in reducing breast cancer risk and improving overall survival after breast cancer diagnosis, especially among postmenopausal women.

Introduction

Breast cancer has surpassed lung cancer to become the most commonly diagnosed cancer worldwide in 2020 [1]. Less than 10% of breast cancers can be attributed to inherited genetic variations [2-6].

Numerous breast cancer risk factors have been identified, including environmental, reproductive and lifestyle factors, some of which are potentially modifiable [7-9]. A substantial number of epidemiologic studies have shown that individual lifestyle factors, such as obesity in postmenopausal women [10,11], moderate to high alcohol consumption [12], and physical inactivity [13] are associated with increased breast cancer risk. Dietary and cigarette smoking habits may also influence risk of breast cancer but results are inconclusive [14-18]. As behavioral factors and lifestyle pattern often cluster together [19,20], it is important to consider these factors simultaneously and to take into account possible synergistic or antagonistic health effects.

The healthy lifestyle index (HLI) is a measurement of multiple recognized modifiable risk factors, or patterns of behavior, and it has been applied to various chronic diseases, including cardiovascular disease [21-24], diabetes [25,26], and various types of cancer [27-29]. Studying the joint effects of modifiable lifestyle factors on chronic diseases is not only essential to improve understanding of the etiology but also facilitate the development of prevention strategies [30]. Previous studies have

investigated the relationship between HLI and breast cancer risk, and found that having a healthy lifestyle was associated with a reduced risk of breast cancer [27,28,31-35,29]. However, these studies used different lifestyle risk factor combinations, different measures and/or cut-points [27,28,31-35].

Furthermore, few studies have explored the association between combined lifestyle behaviors and breast cancer survivorship. One study from the Third National Health and Nutrition Examination Survey (NHANES III) investigated the association between combined lifestyle behaviors and overall mortality in cancer survivors, but did not specify the cancer types [36]. To our knowledge, only one study has explored the joint effect of lifestyle factors on breast cancer survival [37], but the role of HLI in relation to breast cancer survival remains ambiguous. Therefore, based on World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) guidelines [38], we created a comprehensive HLI score combining myriad lifestyle factors, including diet, physical activity, body mass index (BMI), smoking, alcohol consumption and breastfeeding. The purpose of this study is to investigate the association between this HLI and breast cancer risk as well as mortality after breast cancer diagnosis in a population-based breast cancer study.

Materials And Methods

Study population

We utilized the case-control [39] and follow-up [40] studies from the population-based Long Island Breast Cancer Study Project (LIBCSP), which included 1,508 women diagnosed with incident invasive or breast carcinoma *in situ* between August 1, 1996 and July 31, 1997 and 1,556 women without breast cancer who were residents of the same two counties, frequency matched by 5-year age group to the expected age distribution of cases. Potentially eligible control women were identified by Waksberg's method of random digit dialing [41] for those under 65 years of age, and the Health Care Finance Administration (HCFA) rosters for those 65 years and older. Institutional Review Board approval was obtained from all participating institutions and written informed consent was obtained prior to study participation.

This current study included 1,319 cases and 1,310 controls who had complete data on the components of HLI score, including diet, alcohol consumption, physical activity, BMI, and menopausal status. The CONSORT diagram in Supplementary Fig S1 provides the details of the study population. For the 1319 women with breast cancer, vital status was ascertained through linkage with the National Death Index (NDI). They were followed from the time of diagnosis in 1996-1997 through December 31, 2014 to determine the date and cause of death, including death from breast cancer, identified using International Classification of Death codes 174.9 and C-50.9 listed on the death certificate [40]. Over a median follow-up of 214.5 months (range = 2.8 – 224.2 months), we identified 521 deaths, including 210 deaths from breast cancer. Information on the tumor receptor status, including estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor (HER2), was obtained from the pathology records.

Construction of HLI

The information on demographic characteristics, pregnancy history, menstrual history, hormone use, family history of cancer, body size changes, current alcohol use, active and passive cigarette smoking, physical activity, and breastfeeding history were obtained from the main study questionnaire completed at enrollment. A detailed description of the food frequency questionnaire (FFQ) for the LIBCSP, which captured information on diet in the year prior to diagnosis among cases or prior to enrollment among controls, has been published elsewhere [42,43].

The HLI was generated by including information on six lifestyle recommendations (body fatness, physical activity, consumption of plant foods, animal foods, and alcohol, and breastfeeding) based on the new WCRF/AICR guidelines [38] with additional consideration on smoking [18,44]. Each of the HLI components was scored from 0 to 1. Physical activity, alcohol consumption and body fatness were each given a score of 1 point when the recommendation was met, 0.5 points when it was partially met and 0 points otherwise. Because body fatness (BMI calculated as weight (kg)/height (m²)) was inversely associated with breast cancer risk in premenopausal women, but positively associated with breast cancer risk in the postmenopausal women [45], a high HLI score represents high BMI in premenopausal women and low BMI among postmenopausal women. Breastfeeding was assigned a score of 0 for no history of breastfeeding or 1 for having a history of breastfeeding. Intake of plant foods was scored based on recommendations of the intake of fruits/vegetables (score = 0, 0.25, or 0.5, for recommendation not met, partially met, and fully met, respectively), beans (score = 0, 0.15, or 0.25) and whole grains (score = 0, 0.15, or 0.25). Intake of animal foods was scored based on the intake of red meat and processed meat (score = 0, 0.25, 0.5). Consistent with previous studies [46,32,47,31,35,33], smoking was included in the HLI score and scored as 1 for being never smokers, 0.5 for being a former smoker who quit more than 12 months before reference date, or 0 points for being a current smokers at or within 12 months of the reference date. The scoring system was based on the assumption that each major recommendation would contribute equally to the study outcomes. Therefore, the total HLI score can be ranged from 0 to 7, with higher scores indicating a healthier lifestyle. Detailed information on the operationalization of HLI score can be found in Supplementary Table S1. Based on the HLI score distribution of the controls, we then categorized the study population into tertiles as low, intermediate, and high HLI groups.

Statistical Analyses

The general characteristics of cases and controls were compared using independent samples Student's t test or Wilcoxon test for continuous variables and chi-square for categorical variables. An unconditional multivariable logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for associations between HLI scores and incident breast cancer. HLI scores were modeled as a continuous (1-point increment) and categorical variables (tertiles) with the low tertile of HLI score serving as the reference group in the categorical analyses. All models were adjusted for reference age (continuous in years; age at diagnosis for cases and age at study enrollment for controls). Potential confounders of the association between healthy lifestyle and breast cancer risk or mortality included: family history of breast cancer in a first-degree relative, education and parity. Starting from fully adjusted models, none of these variables altered the OR or HR estimates by more than 10%; therefore, only age-

adjusted results are presented. Separate models were also fitted according to the breast cancer subtypes (i.e. hormone receptor (ER and PR) and HER2 receptor status). Cox regression models were used to estimate the hazard ratios (HRs) and 95% CIs for all-cause and breast cancer-specific mortality in association with HLI scores. Similar to logistic regression analyses mentioned above, only age-adjusted results reported. We also performed stratified analyses by menopausal status and tumor subtypes. Sensitivity analyses were performed with the different weights for fruits/vegetables, beans, whole grains, red meat and processed meat in HLI food score. These sensitivity analyses did not materially alter the results. The analyses were carried out using glm (generalized linear model) function, and the “survival” and “forestplot” packages in R version 3.6.1 [48-50]. All tests were two-tailed, and P values <0.05 were considered statistically significant.

Results

The distributions of the population characteristics of cases and controls are shown in Table 1. Compared to the controls, the cases were older, less educated, with lower parity, and greater family history of breast cancer. For the individual components of the HLI score, there were no significant differences between cases and controls except that cases had a lower prevalence of a history of lactation (31.9% vs 35.7%, $P = 0.043$). The median HLI score was significantly higher in controls than in cases (3.25 vs. 3.00, $P < 0.001$). When stratified by menopausal status, the difference in HLI scores between cases and controls was only statistically significant in postmenopausal ($P < 0.001$) but not premenopausal women (Supplementary Table S2).

Table 1. Demographic characteristics of participants in the Long Island Breast Cancer Study Project, 1996-1997

Characteristics	Controls (N = 1310)	Cases (N = 1319)	P values*
Age at reference, mean (SD)	58.5 (12.7)	56.9 (12.7)	< 0.001
Age at menarche, mean (SD)	12.6 (1.6)	12.6 (1.6)	0.745
Race (%)			
White	1240 (94.1)	1214 (92.7)	0.143
Black	57 (4.3)	61 (4.7)	
Others	21 (1.6)	35 (2.7)	
Education level (%)			
Less than high school	160 (12.2)	123 (9.4)	0.027
High school graduate	480 (36.5)	448 (34.3)	
Some college	308 (23.4)	336 (25.7)	
College graduate	162 (12.3)	199 (15.2)	
Post-college	206 (15.7)	202 (15.4)	
Family history**, yes (%)	265 (20.7)	174 (13.6)	< 0.001
Menopausal status, premenopausal (%)	878 (66.6)	853 (65.1)	0.457
Parity status, mean (SD)	2.4 (1.5)	2.6 (1.7)	0.001
OC use, ever (%)	579 (44.0)	597 (45.6)	0.419
HRT use, ever (%)	347 (26.3)	319 (24.4)	0.258
Healthy lifestyle factors			
Plant food consumption, mean (SD)	0.39 (0.26)	0.41 (0.26)	0.071
Animal food consumption, mean (SD)	0.05 (0.11)	0.05 (0.13)	0.395
Alcohol users, (%)	805 (61.0)	805 (61.5)	0.857
Physical activity, > 0.7hrs/week, (%)	614 (46.6)	645 (49.2)	0.180
BMI, mean (SD)	26.59 (5.61)	26.34 (5.71)	0.270
Smoker, (%)	723 (54.8)	706 (53.9)	0.664
Lactation, ever (%)	421 (31.9)	468 (35.7)	0.043
HLLI, median (range)	3.00 (0.25 – 6.05)	3.25 (0.50 – 6.50)	< 0.001

HLI			
Low (< 2.75)	496 (37.6)	411 (31.4)	0.002
Intermediate (2.75 – 3.65)	447 (33.9)	463 (35.3)	
High (> 3.65)	376 (28.5)	436 (33.3)	

HRT = hormone replacement therapy; OC = oral contraceptive; HLI = Healthy Lifestyle Index; BMI = Body Mass Index

* *P* values are from Student’s *t* test for continuous variables and chi-square for categorical variables;

** Family history of first degree relative.

Compared to women in the low HLI tertile, women with higher HLI scores had a decreased odds of breast cancer (intermediate: OR = 0.78, 95% CI = 0.65 – 0.94; high: OR = 0.68, 95% CI = 0.56 – 0.83). Modeled as a continuous variable, a one-point increase in the HLI score was associated with a breast cancer OR of 0.85 (95% CI = 0.79 – 0.92). As shown in Fig 1A, these inverse associations were more pronounced and only statistically significant only among postmenopausal women. When stratified by tumor hormone receptor status (Fig 1B), the high versus low tertile of HLI was inversely associated with breast cancer in women with ER⁺/PR⁺ tumors (OR = 0.61, 95% CI = 0.47 – 0.78). The association was similar for both HER2⁺ (OR = 0.82, 95% CI = 0.70 – 0.96) and HER2⁻ (OR = 0.84, 95% CI = 0.76 – 0.94) tumors. There were no statistically significant associations between HLI and ER⁻/PR⁻ or triple-negative breast cancer (TNBC) tumors.

In survival analyses, we examined the HLI in relation to both overall and breast cancer-specific mortality. Among the 1319 women with breast cancer, 521 deaths were reported during the 15+ years of follow-up (median duration of follow-up = 214.5 months, range, 2.8 – 224.2 months); 210 (40.3 %) died of breast cancer. The 5-, 10-year and 15-year survival rate were 88.9% (95% CI = 87.3 – 90.6 %), 76.7% (95% CI = 74.5 – 79.0 %), and 67.2% (95% CI = 64.7 – 69.8%), respectively. Compared to women in the low HLI tertile, women with higher HLI tertile had lower rates of all-cause mortality (intermediate: HR = 0.75, 95% CI = 0.61 – 0.91; high: HR = 0.74, 95% CI = 0.60 – 0.92) (Fig 2A). Additionally, a one-point increase of HLI score was associated with a decreased all-cause mortality (HR=0.83; 95% CI = 0.76 – 0.91). These inverse associations were significant only among postmenopausal women (Fig 2A). With respect to breast cancer-specific mortality (Fig 2B), no statistically significant associations with HLI were observed; however, there was a suggestive inverse association among postmenopausal women for a one-point increase HLI score (HR = 0.85; 95% CI = 0.71 – 1.01).

Discussion

In this population-based study with long-term follow-up, we observed that a healthy lifestyle was associated with a modest reduction in not only of the risk of developing breast cancer, but also of all-cause mortality after breast cancer, especially among postmenopausal women, who constitute the majority of the breast cancers diagnosed.

There is accumulating evidence associating combined lifestyle factors, or patterns of behavior, to cardiovascular disease [21-24], diabetes [25,26], and various types of cancer [27-29]. Several studies have reported joint effects of common modifiable risk factors on breast cancer risk [28,31-35,29]. These studies have focused on different definitions of healthy lifestyle, used distinct measures and/or cut points, employed various analytical techniques and examined populations from different geographical areas.

Using a similar HLI score as ours, investigators of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort reported a lower breast cancer risk (HR = 0.84, 95% CI: 0.78 – 0.90) for women with a high HLI score [34]. In another study from the same cohort, McKenzie and colleagues used a breast cancer specific health index and reported that women in the highest versus the lowest category had an even greater reduced risk (HR = 0.74, 95% CI: 0.66 – 0.83) of postmenopausal breast cancer [33]. Similarly, the Canadian Study of Diet, Lifestyle, and Health demonstrated that postmenopausal women with a high HLI score had a 30% reduction in the risk of breast cancer (HR = 0.70, 95% CI: 0.53 – 0.93) and each unit increase in the HLI score was associated with a 3% reduction [47]. Our results in the LIBCSP population are comparable to these published results.

The inverse associations between HLI and breast cancer risk were statistically significant only among postmenopausal women in this study. These findings are consistent with previously published studies. A case-control study conducted by McKenzie et al. reported reduced breast cancer risk with high HLI scores (OR = 0.47, 95% CI = 0.23 – 0.94) only in postmenopausal women in New Zealand [32]. Two other studies found a stronger effect of healthy lifestyle on the risk of breast cancer among postmenopausal women than premenopausal women. A study conducted in Morocco by Khalis et al. showed that a one-point increment in HLI score was inversely associated with risk of breast cancer among all women (OR = 0.44, 95% CI = 0.32 – 0.61), as well as premenopausal (OR = 0.51, 95% CI = 0.37 – 0.70) and postmenopausal women (OR = 0.41, 95% CI = 0.28 – 0.60) [31]. A case-control study in Mexican women found the highest quintile of HLI had significantly lower breast cancer risk than those in the lowest quintile (premenopausal OR = 0.5, 95% CI = 0.29 -0.84; postmenopausal OR = 0.20, 95% CI = 0.11 – 0.37) [35].

However, we note that we may have been underpowered to detect an association between HLI score and premenopausal breast cancer risk given the relatively small number of premenopausal women included in our study. The fact that all point estimates (ORs) were less than one regardless of menopausal status suggests that a healthy lifestyle may be beneficial for both premenopausal and postmenopausal women. Another possibility is that genetics (such as *BRCA1* mutations) plays a more important role in early onset breast cancer [51,52]. Therefore, the influence of lifestyle factors may be less prominent in premenopausal women. However, studies investigating this hypothesis are needed.

Our findings suggest that a healthy lifestyle is associated with reduced risk of ER⁺/PR⁺ tumors (OR = 0.61, 95% CI = 0.47 – 0.78), which constitutes approximately 70% of breast tumors[53]. This finding is in line with previous studies; Arthur et al. reported that women in the highest HLI score quintile had a reduced risk for ER⁺/PR⁺ tumors compared with those in the lowest quintile (HR = 0.63, 95% CI = 0.57 –

0.69) [54]. McKenzie et al. also demonstrated an inverse association between HLI score and risk of ER⁺/PR⁺ cancers [33]. We also observed an inverse association between HLI score and ER⁻/PR⁻ and TNBC tumor, but our findings were not statistically significant, which may also be due to small size. Similar to our study, Romaguera and colleagues found a non-statistically significant inverse association between a healthy lifestyle and risk of TNBC [29]. This might be explained by TNBC being associated with a young age at diagnosis and the three common founder mutations in the highly penetrant cancer susceptibility genes *BRCA1* and *BRCA2* (*BRCA1/2*) [55].

The association between combined lifestyle behaviors and breast cancer survivorship has not been investigated extensively. There is only one previous study from a population-based cohort in Norway that explored the joint effect of lifestyle factors on breast cancer survival and reported that an unfavorable lifestyle was associated with a higher overall mortality risk [37]. The combined lifestyle factors included BMI, physical activity, alcohol use, smoking and hypertension. Another study from NHANES III found lower all-cause mortality associated with increased HLI score for cancer survivors (HR = 0.81, 95% CI = 0.72 – 0.90, per 1 unit increase) [36]; however, the report did not specify the cancer type. In our study, a one-point HLI score increase was associated with a reduced all-cause mortality for breast cancer survivors (HR = 0.83, 95% CI = 0.76 – 0.91). The components of HLI in NHANES III were similar to those used in our study: being a never smoker, lifetime healthy body weight maintenance, practicing moderate to vigorous physical activity, moderate alcohol consumption and high diet quality; however, breastfeeding, which is specific to breast cancer, was not included.

Our study has several strengths. All the breast cancer cases were confirmed and centrally adjudicated using medical records and pathology reports. The other strength is the population-based study design which enhances the ability to generalize to other populations. However, our study has some limitations. First, differential recall bias between cases and controls is one inherent limitation of all case-control studies. Second, breast cancer diagnosis or its treatments may also alter the lifestyle patterns. However, only incident cases were recruited prior to any major treatment, which may minimize such bias. Third, we did not have sufficient information to include all recommendations in the guidelines of WCRF/AICR cancer prevention [8], such as the intake of supplements for cancer prevention. However, the findings using our modified HLI score are consistent with those from studies based on WCRF/AICR guidelines. Fourth, the index components were equally weighted, without taking into account the unequal impact of each factor on cancer risk, but analyses with different weights for food component yielded similar results. Lastly, survivorship may be influenced by treatment and tumor clinical characteristics of which information is lacking in the LIBCSP population, which may influence lifestyle behaviors and diet.

Conclusion

Our results strongly support the hypothesis that a healthy lifestyle may reduce the risk of breast cancer as well as improve survival after breast cancer, especially in postmenopausal women. These findings support lifestyle-based prevention and intervention strategies to reduce the disease burden of breast cancer.

Declarations

Financial support

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Conflict of interest

Dr. Neugut has consulted for Otsuka, GlaxoSmithKline, Eisai, Hospira, and United Biosource Corp. He is a member of the Medical Advisory Board of EHE Intl. All other authors declare that they have no conflict of interest.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

The codes used to analyze the datasets during the current study are available from the corresponding author on reasonable request.

Contributions

Conception and design of the study was conducted by QL, JC and ST. Analysis and interpretation of data was conducted by QL. The draft of the manuscript was written by QL. CL, AN, RS, HP, ST and JC reviewed the data and participated in revising the manuscript. All authors read and approved the final manuscript.

Ethical approval

Institutional Review Board approval was obtained from all participating institutions.

Informed consent

All participants provided written informed consent prior to study participation.

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Figures

Figure 1

Odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between health lifestyle index score and risk of breast cancer in the Long Island Breast Cancer Study Project. A. stratified by menopausal status; B. stratified by hormone receptor.

Figure 2

Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between health lifestyle index score and all-cause and breast cancer-specific mortality in the Long Island Breast Cancer Study Project. A. all-cause death; B. breast cancer-related death.

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