Research Article

Cancer Prevention Research

The Combined Association of Modifiable Risk Factors with Breast Cancer Risk in the Women's Health Initiative

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Abstract

Although several modifiable risk factors have been independently associated with risk of breast cancer, few studies have investigated their joint association with breast cancer risk. Using a healthy lifestyle index (HLI) score, we assessed the association of a combination of selected modifiable risk factors (diet, alcohol, physical activity, BMI, and smoking) with risk of invasive breast cancer in the Women's Health Initiative (WHI). This study comprised 131,833 postmenopausal women, of whom 8,168 had breast cancer, who were enrolled in the WHI Observational Study or the WHI clinical trials. Cox proportional hazards regression was used to estimate the HRs and 95% confidence intervals (CI) for the association of the score with the risk of developing breast cancer overall and according to specific breast cancer clinicopathologic characteristics. There was a 4% reduction in the risk of breast cancer per unit increase in the HLI score. Compared with those with an HLI score in the lowest quintile level, those in the highest quintile level had 30%, 37%, and 30% lower risk for overall, ER^+/PR^+, and $HER2^+$ breast cancer, respectively (HR = 0.70; 95% CI, 0.64–0.76; 0.63, 0.57–0.69; and 0.70; 0.55–0.90, respectively). We also observed inverse associations between the score and risk of breast cancer irrespective of nodal status, tumor grade, and stage of the disease. Most individual lifestyle factors were independently associated with the risk of breast cancer. Our findings support the view that promoting healthy lifestyle practices may be beneficial with respect to lowering risk of breast cancer among postmenopausal women. *Cancer Prev Res; 11(6); 317–26. ©2018 AACR.*

See related editorial by Friedenreich and McTiernan, p. 313

Introduction

Modifiable risk factors are believed to play an important role in breast carcinogenesis. In this regard, the Women's Health Initiative (WHI) cohort, one of the largest prospective studies, to date, to investigate the role of lifestyle-related factors in the etiology of breast cancer, has demonstrated that obesity, moderate to high alcohol consumption, physical inactivity, and smoking are associated with increased risk of postmenopausal breast cancer (1–6). Other epidemiologic studies have also shown positive associations of postmenopausal obesity, alcohol consumption, physical inactivity, and smoking with risk of breast cancer (6–11). With regards to diet, there is limited evidence to suggest that it has a major effect on a woman's risk of breast cancer. In the WHI dietary modification trial, a low-fat dietary pattern was weakly associated with decreased risk of breast cancer (5, 6), whereas other recent studies have found that certain dietary patterns, such as the prudent/healthy dietary pattern (characterized by high intake of high fiber foods such as cereals, fruits, and vegetables, no more than moderate alcohol consumption, and low amounts of red meat, poultry, and dairy products), are associated with reduced risk of breast cancer, thus suggesting that diet may also influence risk (12–14).

Although the independent associations of the aforementioned modifiable factors with risk of breast cancer have been widely studied, few studies have examined their joint association with risk of this disease. As an individual's lifestyle behaviors typically cluster, it is likely that these risk factors act jointly rather than independently to influence the risk of breast cancer (15, 16). In support of this concept, several epidemiologic studies have shown that adherence

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to general cancer prevention guidelines (i.e., maintaining a healthy weight; exercising regularly; limiting consumption of energy-dense foods, red meats/processed meats, high sodium foods and alcoholic beverages; consuming a variety of vegetables, fruits, whole grains and legumes) is associated with reduced risk of breast cancer (8, 10, 17). Other studies have also sought to address the combined effect of modifiable risk factors on risk of breast cancer using a healthy lifestyle index (HLI) score, which is characterized as a combination of five recognized modifiable risk factors that are associated with chronic diseases, namely diet, alcohol, physical activity, body mass index (BMI) and smoking (18). To our knowledge, only four studies, two of which were cohort studies, have examined the association between this score and risk of breast cancer, and, in keeping with the findings of studies based on *World Cancer Research Fund/ American Institute for Cancer Research (WCRF/AICR) guidelines*, inverse associations were seen (18–21).

Studying the joint association of modifiable factors with risk of breast cancer is not only essential to improve our understanding of the etiology of the disease but, from a public health perspective, may also facilitate the development of breast cancer prevention strategies (15). Given the limited data from prospective studies on the joint association of the aforementioned modifiable factors with risk of breast cancer, we studied the association of a HLI score, as defined previously (18), with the risk of developing invasive breast cancer in the large, well-characterized WHI cohort. Furthermore, given that factors that influence risk of developing breast cancer have been suggested to have differential effects across breast tumor clinicopathologic characteristics (hormone receptor status, nodal status, grade, stage; refs. 22, 23), we examined the association between the HLI score and risk by levels of these characteristics. However, to date, to our knowledge, only one study has investigated the association between the HLI score and risk of breast cancer subtypes defined by various clinicopathologic characteristics (19). Therefore, we also assessed the association of score with breast cancer clinicopathologic characteristics (receptor status, lymph node, grade, stage).

Materials and Methods

Study population and design

A detailed description of the WHI design and study population has been published previously (24). Briefly, this large, multicenter study comprised 161,808 postmenopausal women ages 50 to 79, from major racial/ethnic groups, who were enrolled at 40 clinical centers throughout the United States between 1993 and 1998. The study was designed to include a Clinical Trial (CT) with three overlapping components [hormone therapy (2 trials), low-fat diet modification, and calcium–vitamin D supplementation; $n = 68{,}132$] and an Observational Study (OS) component ($n = 93{,}676$; ref. 24). For the current study, women from the dietary intervention group ($n = 19{,}541$), who were required to reduce their intake of energy-dense foods while increasing their intake of low-calorie foods (specifically fruits and vegetables and grain products), were excluded as their baseline diet measurements would not have captured those dietary changes (25). Women were also excluded if they did not have information on follow-up time ($n = 443$), if they had breast cancer *in situ* ($n = 14$), if their estimated energy intake was deemed to be implausible (<600 kcal/d or >5,000 kcal/d; $n = 4{,}602$) or if they had a previous history of breast cancer ($n = 5{,}375$). After exclusion, our study comprised 131,833 ($n = 84{,}476$ and $n = 47{,}357$ from the OS and CT, respectively) postmenopausal women who were followed up until September 30, 2016.

Exposure and covariates ascertainment

Baseline information on demographic characteristics, menstrual history, reproductive history, exogenous hormone use, family history, medical history, and diet and lifestyle factors was collected from the study participants using self-administered questionnaires. Dietary intake was assessed using a food frequency questionnaire comprising 122 foods, including alcohol, and food groups. Participants were asked to report their usual frequency of intake (from "never or less than once per month" to "2+ per day" for foods and "6+ per day" for beverages) and portion size (small, medium, or large compared with the stated medium portion size). The reliability of the FFQ was assessed by calculating intraclass correlation coefficients between the first and second administration of the questionnaire (i.e., at or before first clinic visit and after enrollment). The mean correlation coefficient for selected nutrients was 0.76 (26). With regards to smoking habits, participants were asked whether they had ever smoked. Current and former smokers reported age at smoking initiation, number of cigarettes smoked daily, years of smoking, and age at quitting smoking (former smokers only). Participants' weight and height measurements were taken by trained staff at baseline. Weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm. BMI was computed as weight in kilograms divided by height in meters squared. Questions on physical activity level were designed to capture the participants' usual activity or patterns of activity, including walking and sports. Metabolic equivalent (MET)-hours/week was then computed by multiplying the number of hours per week of leisure–time physical activity by the MET value of the activity and summing the products of all types of activities (3).

The HLI score

We created an *a priori* HLI score based on both existing scientific knowledge that suggests that diet, alcohol consumption, physical activity, BMI, and smoking influence cancer development and on public health recommendations for cancer prevention (6–11). Unlike scores based on the *WCRF/AICR guidelines*, which focuses on whether or not a person adheres to approximately ten general cancer

prevention guidelines (10), this simple score is based on a combination of several levels (each individual HLI component had five categories) of five most common modifiable risk factors, which allowed us to assess dose–response relationships between the exposures and the outcomes. The HLI score was calculated using information on five modifiable risk factors, namely diet, alcohol consumption, physical activity, BMI, and smoking, as described elsewhere (18). To generate the dietary component of the HLI score, we used information on intake of fruits and vegetables, grains, red and processed meat, the ratio of polyunsaturated to saturated fat, trans-fats, and glycemic load, to create a diet score. Specifically, to generate the score, the residuals from the linear regression models of each of the aforementioned dietary components on total energy intake were categorized into deciles and scored from 0 (lowest decile) to 9 (highest decile; vice versa for red/processed meat, trans-fat, and glycemic load). The individual scores were then totaled and categorized into quintiles (18). The HLI score was then constructed by summing the scores of diet (5th quintile = 4, 4th quintile = 3, 3rd quintile = 2, 2nd quintile = 1, 1st quintile = 0), and other lifestyle factors (smoking: never smoked = 4, ex-smokers quit $\leq$ 10 years = 3, ex-smokers quit > 10 years = 2, current smoking $\leq$ 15 cigarettes/day = 1, current smoking > 15 cigarettes/day = 0; alcohol intake (g/day): none = 4, >0.0–4.9 = 3, >4.9–9.9 = 2, >9.9–19.9 = 1, >19.9 = 0; physical activity based on metabolic equivalent tasks [5th quintile = 4, 4th quintile = 3, 3rd quintile = 2, 2nd quintile = 1, 1st quintile = 0; and BMI (kg/m^2): 18.5–24.9 = 4, <18.5 = 3, 25.0–29.9 = 2, 30.0–34.9 = 1, 35+ = 0]. The final score ranged from 0 to 20 with 20 being the healthiest behavior. The healthiest behavior was characterized by consuming a healthy diet (5th quintile), avoidance of smoking, no alcohol consumption, high physical activity level (5th quintile), and a healthy BMI (18.5–24.9 kg/m^2).

Outcome ascertainment

Women were contacted semiannually in the CT groups and annually in the OS group, using in-person, mailed, or telephone questionnaires, to obtain information on clinical outcomes. Breast cancer cases were confirmed centrally by trained physician adjudicators who reviewed medical records and pathology reports. Coding of breast cancer characteristics (tumor hormone receptor status, histology, nodal involvement, grade, and stage) was performed using the NCI's Surveillance Epidemiology and End Results coding system (27). A total of 8,168 incident invasive breast cancers were ascertained by the end of the follow-up.

Vital status was collected through follow-up of participants and proxies and periodic searches of the National Death Index. Cause of death was determined by medical record and death certificate review.

Statistical analysis

Medians (interquartile range) and frequencies were calculated to summarize the characteristics of the population. We used Cox proportional hazards models to estimate HRs and 95% confidence intervals (CI) for the association between the HLI score and risk of invasive breast cancer. The outcome was time to diagnosis of invasive breast cancer. Participants were censored (noncases) if they died, withdrew from the study before the end of follow-up, or did not develop invasive breast cancer by the end of follow-up (September 30, 2016). Cases contributed person-time to the study from their date of enrollment until the date of diagnosis of breast cancer, and noncases contributed person-time from their date of enrollment until date of death, date of withdrawal from the study or until the end of follow-up, whichever came first. Similar analyses were conducted to examine the association of the HLI score with breast cancer risk within strata defined by clinicopathologic characteristics. For these latter analyses, we additionally censored the outcomes (i.e., ER^+/PR^+, ER^+/PR^-, ER^-/PR, $HER2^+$, HER^-, well-differentiated, moderately differentiated, poorly differentiated, localized or regional/distant tumor, or tumors with positive or negative lymph node) that were not in the event group of interest. Our analyses did not include women with ER^-/PR^+ tumors due to the small number of women with this subtype. The association of the HLI score with risk of breast cancer by hormone therapy status, family history of breast cancer, and ethnicity was also assessed. All regression models (except for analyses stratified by risk factors) were adjusted for age at entry (continuous), ethnicity (white, black, other), height (continuous), education (high school or less/postsecondary or some college, graduate school or some graduate school), family history of breast cancer in first-degree relative (yes, no), age (years) at menarche (>12, 12–13, 14+), parity (never been pregnant or no term pregnancy, 1, 2, 3, 4+), breastfeeding (yes, no), history of mammograms (yes, no), age (years) at menopause (>45, 45–54, >55), hormone replacement therapy (HT) use (never, past, current), oral contraceptive use (yes, no), history of benign breast disease (yes, no), and nonalcohol energy intake (continuous); for the stratified analyses, the models included all of these variables except the stratification variable. To test whether the association of breast cancer with the HLI score differed across breast cancer clinicopathologic characteristics, we performed likelihood ratio tests whereby we compared the likelihood ratios of Cox proportional hazards models with and without an interaction term (i.e., interaction between the exposure and breast cancer clinicopathologic characteristics; ref. 28). When the individual components of the HLI score were included as the main exposures, the models were also adjusted for the other individual components of the score. Tests for trend were performed by assigning an ordinal number to each of the categories of the HLI score, which was then modeled as a continuous variable, and Wald tests were used to assess statistical significance. The proportional hazards assumption was tested in the Cox regression

Table 1. Characteristics of women from the Women's Health Initiative Study, 1993–2016 ($N = 131,833$)

	Breast cancer	
	Yes ($n = 8,168$)	**No ($n = 123,665$)**
Age at entry [yrs.; median (IQR)]	63 (57–69)	63 (57–68)
Ethnicity: *n* (%)		
White (not of Hispanic origin)	7228 (88.5)	102,870 (83.2)
Black or African-American	480 (5.9)	10,394 (8.4)
Other	444 (5.4)	10,091 (8.2)
Missing	16 (0.2)	310 (0.3)
Height [cm; median (IQR)]	162.6 (158.4–166.6)	161.8 (157.5–166.0)
Education: *n* (%)		
High school or less	3,703 (43.6)	48,693 (39.4)
Postsecondary/some college	2,943 (36.1)	46,381 (37.5)
Graduate school/some graduate school	1,463 (17.9)	27,656 (22.4)
Missing	59 (0.7)	935 (0.8)
Family history of breast cancer in first-degree relative: *n* (%)	1,864 (22.8)	20,926 (16.9)
Age at menarche (y): *n* (%)		
<12	1,894 (23.2)	26,887 (21.7)
12—13	4,538 (55.6)	67,732 (54.8)
≥14	1,704 (20.9)	28,546 (23.1)
Missing	32 (0.4)	500 (0.4)
Parity: *n* (%)		
Never been pregnant/no term pregnancy	1,107 (13.6)	14,523 (11.7)
1	714 (8.7)	10,760 (8.7)
2	2,129 (26.1)	30,744 (24.9)
3	1,974 (24.2)	29,681 (24.0)
4+	2,191 (26.8)	37,145 (30.0)
Missing	53 (0.7)	812 (0.7)
Breastfed: *n* (%)	4,172 (51.1)	62,962 (50.9)
Age at menopause (y): *n* (%)		
<45	1,642 (20.1)	29,469 (23.8)
45—54	4,749 (58.1)	69,103 (55.9)
≥55	1,059 (13.0)	13,286 (10.7)
Missing	718 (8.8)	11,807 (9.6)
Ever had mammogram: *n* (%)	8,041 (98.5)	120,831 (97.7)
HT use: *n* (%)		
Never	3,166 (38.8)	53,770 (43.5)
Past	1,128 (13.8)	19,517 (15.8)
Current	3,866 (47.3)	50,268 (40.7)
Missing	8 (0.1)	110 (0.1)
Oral contraceptive: *n* (%)	3,537 (43.3)	50,904 (41.2)
History of benign breast disease: *n* (%)	2,171 (26.6)	25,243 (20.4)
Nonalcohol energy intake [kcal/dy; median (IQR)]	1,508.1 (1,170.5–1,918.8)	1,480.0 (1,137.5–1,903.45)
HLI score [median (IQR)]	9 (12–14)	10 (12–14)
Diet score [units; median (IQR)]	26 (22–32)	26 (21–32)
Alcohol [g/dy; median (IQR)]	1.4 (0.0–7.4)	1.0 (0.0–6.5)
Physical activity [Met-hours/week; median (IQR)]	9.0 (2.5–18.0)	8.8 (2.5–18.5)
BMI [kg/m^2; median (IQR)]	27.0 (23.8–31.2)	26.7 (23.6–30.8)
Smoking status: *n* (%)		
Never	3,884 (47.6)	62,219 (50.3)
Ex-smokers quit ≥10 y	3,114 (38.1)	42,860 (34.7)
Ex-smokers quit <10 y	549 (6.7)	8,376 (6.8)
Current ≤ 15 cigs/day	39 (0.5)	728 (0.6)
Current > 15 cigs/day	479 (5.9)	7,857 (6.4)
Missing	103 (1.3)	1,625 (1.3)

Abbreviations: IQR, interquartile range; Met, metabolic equivalent.

models using Schoenfeld residuals. There was no evidence of violation of the proportional hazards assumption.

All statistical analyses were performed using Stata 14.1 (StataCorp). *P* values are two-sided.

Results

After a median follow-up duration of 16.9 years, the cumulative person-years for the total study population was 1,875,202.7. Table 1 provides a summary of the baseline characteristics of the study population. Compared with women without breast cancer, women who developed breast cancer had slightly higher median alcohol intake, physical activity level, and BMI, but were slightly less likely to report being current smokers than women without breast cancer (Table 1). The median age and HLI and diet scores were, however, similar in both groups.

The associations of the HLI score with risk of breast cancer overall and according to breast cancer characteristics are presented in Table 2. Compared with those in the

Table 2. Associations between healthy lifestyle score and risk of breast cancer among women from the Women's Health Initiative Study, 1993–2016

	Quintiles												
	≤9		10—11		12–13		14–15		≥16				
	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	P_{trend}	$P_{hetero-geneity}$	Continuous (per unit increase in score)
All breast cancer cases	1,825	1.00	1,662	0.93 (0.87–1.00)	1,761	0.85 (0.80–0.91)	1,746	0.75 (0.70–0.81)	1,369	0.70 (0.64–0.76)	<0.01		0.96 (0.95–0.97)
Receptor status													
ER+/PR+	1,233	1.00	1,085	0.89 (0.82–0.97)	1,167	0.82 (0.76–0.89)	896	0.72 (0.65–0.78)	659	0.63 (0.57–0.69)	<0.01		0.95 (0.94–0.96)
ER+/PR−	205	1.00	213	1.05 (0.87–1.28)	204	0.87 (0.71–1.06)	197	0.95 (0.78–1.16)	159	0.92 (0.74–1.14)	0.26		0.99 (0.97–1.01)
ER−/PR−	212	1.00	202	1.03 (0.85–1.25)	222	1.02 (0.84–1.24)	159	0.85 (0.69–1.05)	133	0.86 (0.69–1.09)	0.09	0.40	0.98 (0.96–1.01)
HER2													
Positive	191	1.00	176	0.95 (0.78–1.17)	166	0.78 (0.63–0.96)	141	0.75 (0.60–0.94)	112	0.70 (0.55–0.90)	<0.01		0.95 (0.93–0.98)
Negative	1,197	1.00	1,081	0.92 (0.85–1.00)	1,162	0.86 (0.79–0.93)	895	0.75 (0.69–0.82)	665	0.67 (0.60–0.73)	<0.01	0.47	0.96 (0.95–0.97)
Triple negative	125	1.00	118	1.02 (0.79–1.32)	139	1.08 (0.85–1.39)	93	0.85 (0.64–1.12)	71	0.78 (0.58–1.07)	0.07		0.96 (0.95–1.00)
Positive lymph node													
Yes	629	1.00	563	0.92 (0.82–1.03)	555	0.79 (0.71–0.89)	444	0.73 (0.64–0.82)	368	0.73 (0.64–0.83)	<0.01		0.96 (0.95–0.98)
No	1,172	1.00	1,083	0.94 (0.87–1.02)	1,174	0.88 (0.81–0.96)	913	0.77 (0.71–0.85)	690	0.70 (0.63–0.77)	<0.01	0.29	0.96 (0.95–0.97)
Grade													
Well-differentiated	443	1.00	418	0.94 (0.82–1.07)	490	0.93 (0.82–1.07)	377	0.80 (0.70–0.92)	272	0.68 (0.58–0.80)	<0.01		0.95 (0.95–0.98)
Moderately differentiated	731	1.00	706	0.98 (0.88–1.09)	707	0.85 (0.76–0.94)	556	0.76 (0.67–0.85)	470	0.76 (0.67–0.86)	<0.01		0.97 (0.95–0.98)
Poorly differentiated	433	1.00	367	0.90 (0.78–1.03)	382	0.83 (0.72–0.95)	300	0.75 (0.64–0.87)	208	0.63 (0.53–0.75)	<0.01	0.29	0.96 (0.94–0.97)
Stage													
Local	1,305	1.00	1,215	0.94 (0.87–1.02)	1,302	0.87 (0.80–0.94)	1,040	0.79 (0.72–0.85)	790	0.71 (0.65–0.78)	<0.01		0.97 (0.96–0.97)
Regional/distant metastatic	471	1.00	420	0.94 (0.82–1.07)	412	0.81 (0.71–0.93)	302	0.68 (0.59–0.79)	252	0.69 (0.59–0.81)	<0.01	0.69	0.96 (0.94–0.97)

NOTE: Adjusted for age at entry, education, nonalcohol energy intake, ethnicity, age at menarche, parity, breastfeed, history of mammograms, HT status, oral contraceptive use, age at menopause, family history, and history of BBD.

Table 3. Associations between the HLI score and risk of breast cancer by ethnicity, and family history among women from the Women's Health Initiative Study, 1993–2016

	HT use			Ethnicity			Family history	
	Never	Past	Current	White	Black	Other	Yes	No
Continuous (per unit score)	0.96 (0.93–1.00)	0.96 (0.95–0.98)	0.96 (0.95–0.97)	0.96 (0.95–0.97)	0.98 (0.95–1.00)	0.96 (0.93–1.00)	0.96 (0.95–0.98)	0.96 (0.95–0.98)
Quintiles								
≤9 points								
No. of cases	813	305	706	1,599	152	72	390	881
HR (95% CI)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
10–11 points								
No. of cases	648	230	782	1,475	107	79	394	743
HR (95% CI)	0.89 (0.81–0.99)	0.80 (0.68–0.96)	1.02 (0.92–1.13)	0.93 (0.86–1.00)	0.92 (0.72–1.18)	1.03 (0.75–1.43)	1.00 (0.87–1.15)	0.90 (0.82–1.00)
13–14 points								
No. of cases	659	229	857	1,544	92	105	391	730
HR (95% CI)	0.84 (0.75–0.93)	0.70 (0.58–0.83)	0.92 (0.83–1.02)	0.83 (0.78–0.90)	0.86 (0.66–1.13)	1.04 (0.77–1.42)	0.88 (0.76–1.02)	0.84 (0.74–0.91)
14–15 points								
No. of cases	492	159	716	1,220	62	83	320	544
HR (95% CI)	0.76 (0.68–0.86)	0.57 (0.47–0.69)	0.82 (0.74–0.91)	0.75 (0.69–0.81)	0.78 (0.57–1.06)	0.84 (0.60–1.17)	0.79 (0.67–0.92)	0.75 (0.67–0.84)
≥16 points								
No. of cases	352	120	588	936	40	83	236	392
HR (95% CI)	0.66 (0.58–0.75)	0.54 (0.43–0.67)	0.79 (0.70–0.88)	0.70 (0.64–0.76)	0.74 (0.53–1.09)	0.76 (0.54–1.07)	0.69 (0.58–0.82)	0.72 (0.63–0.81)
P_{trend}	<0.01	<0.01	<0.01	<0.01	0.05	0.05	<0.01	<0.01
$P_{interaction}$	0.74			0.78			0.76	

NOTE: Adjusted for age at entry, education, nonalcohol energy intake, ethnicity, age at menarche, parity, breastfeed, history of mammograms, HT status, oral contraceptive use, age at menopause, family history, and history of BBD.

lowest quintile level of the HLI score (≤9 points), women in the highest quintile (≥16 points) had a 30% reduced risk of breast cancer (HR = 0.70; 95% CI, 0.64–0.76). There was also a 4% reduction in risk of breast cancer per unit increase in the HLI score (HR = 0.96; 95% CI, 0.95–0.97; Table 2). When considering breast cancer characteristics, inverse associations with hormone receptor double-positive, $HER2^+$, and $HER2^-$ breast tumors, comparable in magnitude with that for all breast cancers combined, were also observed for the highest versus the lowest quintiles of the HLI score (HR = 0.63; 95% CI, 0.57–0.69; HR = 0.70; 0.55–0.90, HR = 0.67; 95% CI, 0.61–0.73 for ER^+/PR^+, $HER2^+$, and $HER2^-$ breast tumors, respectively). Furthermore, there were 5%, 5%, and 4% reductions in risk of hormone receptor double-positive, $HER2^+$, and $HER2^-$ breast tumors, respectively, per unit increase in the HLI score. The HLI score was also inversely associated with risk of ER^+/PR^-, ER^-/PR^- and triple-negative breast cancer breast tumors, although the associations were of borderline statistical significance. Furthermore, having a high HLI score (≥16 points) was associated with reduced risk irrespective of the nodal status, grade, and stage of the tumors.

In analyses stratified by HT status, for all categories (never, past, current), the inverse associations were evident when the HLI score was categorized by quintiles (HR = 0.66; 95% CI, 0.58–0.75, HR = 0.54; 95% CI, 0.43–0.67 and HR = 0.79: 95% CI, 0.70–0.88 for never, past, and current users, respectively; Table 3). There was also an inverse association when the continuous exposure was considered. The HLI score was inversely associated with risk of breast cancer among all ethnicities, although the association was only statistically significant among white women. There was also an inverse association between the HLI score and risk among participants with and without a family history of breast cancer.

With respect to the individual components of the HLI score, having a relatively high physical activity level (>21.5 *MET-hours/wk*) was inversely associated with risk of breast cancer ($HR_{q5\ vs.\ q1} = 0.89$; 95% CI, 0.83–0.96), whereas women with relatively high alcohol intake (>19.9 g/dy; HR = 1.17: 95% CI, 1.07–1.27), overweight and obese women [HR = 1.11; 95% CI, 1.05–1.17, 1.25; 1.17–1.34, 1.45; 1.33–1.57 for overweight (BMI > 25.0–29.9 kg/m^2), moderately obese (BMI = 30–34.9 kg/m^2) and severely obese women (≥35 kg/m^2), respectively], and those who currently smoked more than 15 cigarettes daily (HR = 1.15; 95% CI, 1.04–1.27) had an increased risk of breast cancer (Table 4). A high diet score (>34) had a weak inverse association with risk of breast cancer [$HR_{q5\ vs.\ q1} = 0.95$ (0.88–1.04); $P_{trend} = 0.12$].

Discussion

In this large, well-characterized study population with long-term follow-up, we provide strong evidence that a healthy lifestyle is associated with reduced risk of invasive

Table 4. Associations between HLI score, the HLI components, and risk of breast cancer among women from the Women's Health Initiative Study, 1993–2016

	No. of cases $n = 8{,}168$	HR (95% CI)
Diet score[a]		
1st quintile	1,660	1.00
2nd quintile	2,058	1.04 (0.97–1.12)
3rd quintile	1,634	1.02 (0.95–1.10)
4th quintile	1,542	0.99 (0.92–1.07)
5th quintile	1,274	0.95 (0.88–1.04)
P_{trend}		0.12
Alcohol (g/dy)		
None	1,516	0.99 (0.93–1.05)
>0–4.9	4,021	1.00
>4.9–9.9	943	0.99 (0.92–1.07)
>9.9–19.9	992	1.06 (0.99–1.14)
>19.9	698	1.17 (1.07–1.27)
P_{trend}		<0.01
Physical activity (*MET-hours/wk*)[a]		
1st quintile	1,610	1.00
2nd quintile	1,460	1.00 (0.93–1.07)
3rd quintile	1,588	0.99 (0.92–1.06)
4th quintile	1,635	0.99 (0.92–1.06)
5th quintile	1,514	0.89 (0.83–0.96)
Missing	361	
P_{trend}		0.01
BMI (kg/m^2)		
<18.5	43	0.63 (0.46–0.85)
18.5–24.9	2,712	1.00
25.0–29.9	2,821	1.11 (1.05–1.17)
30.0–34.9	1,533	1.25 (1.17–1.34)
35+	995	1.45 (1.33–1.57)
Missing	64	
P_{trend}		<0.01
Cigarette smoking		
Never	3,884	1.00
Ex-smokers quit $\leq$ 10 years	3,114	1.13 (1.07–1.18)
Ex-smokers quit > 10 years	549	0.99 (0.91–1.09)
Current $\leq$ 15 cigarettes/day	39	1.01 (0.73–1.39)
Current > 15 cigarettes/day	479	1.15 (1.04–1.27)
Missing	103	
P_{trend}		<0.01

NOTE: Adjusted for age at entry, education, non-alcohol energy intake, ethnicity, age at menarche, parity, breastfeed, history of mammograms, HT status, oral contraceptive use, age at menopause, family history, history of BBD, diet, alcohol intake, physical activity, and BMI smoking unless included as main exposure.

Abbreviation: MET = metabolic equivalent.

[a]Cut-off points: Diet score: 0–20, 21–25, 26–29, 30–34, >34; physical activity (*MET-hours/wk*): $\leq$1.5, >1.5–6, >6–12, >12–21.5, >21.5.

breast cancer overall, for most subtypes defined by hormone receptor and HER2 status, and irrespective of the nodal status, grade, or stage of the tumors. The inverse association between the HLI score and risk of breast cancer was also apparent irrespective of HT use, race/ethnicity, and family history of breast cancer.

Except for diet, all components of the HLI score were also associated with risk of breast cancer, consistent with previous findings from the WHI study that postmenopausal women who had relatively high alcohol intake, who were obese, or who smoked cigarettes, had an increased risk of breast cancer, whereas those with a relatively high physical activity level had a reduced risk (1–3, 29). Similar to the findings from the WHI dietary modification intervention study, an intervention study that aimed to evaluate the effect of a low-fat dietary pattern on health-related outcomes, including breast cancer, we observed that diet was only weakly associated with a reduced risk of breast cancer (5, 6). More robust evidence supporting an inverse association between a healthy dietary pattern and risk of breast cancer has been reported in several recent studies (13, 19, 20).

BMI is inversely associated with physical activity (30), and, not surprisingly, other studies also reported that a relatively high physical activity level was associated with reduced risk of breast cancer, whereas obesity has been associated with an increased risk (1, 3, 29, 31). Alcohol consumption has also been shown to be positively associated with risk of breast cancer in several epidemiologic studies (31). Although cigarette smoking is not currently an established risk factor for breast cancer, accumulating epidemiologic evidence also supports our finding of a positive association between smoking and risk of breast cancer, with risk varying with the intensity and duration of smoking (7, 11, 32).

The proportion of breast cancer attributable to modifiable risk factors is generally small, ranging from 2% to 13% (33–37), but studies have indicated that at least 25% to 30% of breast cancer cases may be prevented from an overall healthy lifestyle (38). In keeping with this, our study showed an inverse association between an overall healthy lifestyle and risk of breast cancer. Two large prospective studies by Mc Kenzie and colleagues (18) and Dartois and colleagues (19, 21), and two case–control studies by McKenzie and colleagues (17) and Sánchez-Zamorano and colleagues (19) also found that women with a high lifestyle index score had a reduced risk of breast cancer. In keeping with this, other studies have reported that women who adhered to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and the American Cancer Society (ACS) recommendations (maintaining a healthy weight, being physically active daily, limiting consumption of energy-dense foods, red meats/processed meats, high sodium foods and alcoholic beverages, consuming a variety of vegetables, fruits, whole grains and legumes, and breastfeeding exclusively for up to 6 months) had reduced risk of breast cancer (17, 39–41).

Although some studies have demonstrated that individual components of the HLI score, such as obesity and alcohol consumption, have associations with breast cancer risk that vary by breast tumor characteristics (42, 43), our findings suggest that a healthy lifestyle may be associated with reduced risk of breast cancer irrespective of the tumor characteristics, although the associations were only of borderline statistically significance in some subgroups, perhaps reflecting the relatively small number of cases in those subgroups.

Similar to our study, McKenzie and colleagues demonstrated an inverse association between the HLI score and risk of ER^+/PR^+ tumors (19). The same study also showed that women with a high HLI score had reduced risk of ER^-/PR^- breast cancer (19). Although we also observed an inverse association between the score and this tumor subtype, our findings were statistically nonsignificant. In line with two other studies by Castelló and colleagues (41) and Romaguera and colleagues (40) that used healthy lifestyle scores based on adherence to WCRF/AICR nutritional guidelines, the current study demonstrated that an overall healthy lifestyle was also associated with a reduced risk of $HER2^+$ tumors. Similar to our study, Romaguera and colleagues (40) also found a nonsignificant inverse association between a healthy lifestyle and risk of triple-negative breast cancer. Of note, in the current study, the inverse association was evident across all categories of tumor nodal status, grade, and stage. To the best of our knowledge, no other studies have assessed the association of an overall healthy lifestyle with these breast cancer characteristics. Therefore, our findings need confirmation.

We did not observe an interaction between the HLI score and HT status, race/ethnicity, or family history of breast cancer. This suggests that a healthy lifestyle may contribute to reduced risk of breast cancer among women irrespective of their HT status, ethnicity, and family history of breast cancer. To our knowledge, no study has assessed the association of an overall healthy lifestyle with risk of breast cancer by hormone status. Furthermore, there is a paucity of studies that were conducted to explore the potential modifying effect of ethnicity and family history. In keeping with our findings, Nomura and colleagues (39) and Akinyemiju and colleagues (44) reported that an overall healthy lifestyle was associated with reduced risk of breast cancer among white and black women. In another study by Nomura and colleagues (45), an inverse association was also observed among women without a family history of breast cancer but not among women with a family history of breast cancer.

Biologically, exposures such as relatively high alcohol consumption, physical inactivity, obesity, cigarette smoking, and poor dietary habits (characterized by low intake of potential chemopreventive foods such as fruits and vegetables and high intake of potential cancer-causing foods such as red/processed meat) have been shown to induce processes such as chronic inflammation and oxidative stress, which can subsequently lead to breast carcinogenesis by generating DNA mutations, and stimulating tumor cell growth and proliferation (31, 46). In addition, risk factors such as obesity and alcohol consumption have been associated with risk of hormone-sensitive molecular subtypes of breast cancer (42, 43), which represent the most prevalent hormone receptor subgroups (47). This reflects the fact that these risk factors increase levels of estrogen and insulin-like growth factor, both of which are postulated to influence breast carcinogenesis by stimulating tumor cell proliferation, and generating oxidative DNA damage (38, 48–50).

This study has several strengths. Specifically, it is one of the largest studies to date to investigate the association between a healthy lifestyle and risk of breast cancer overall, and for subgroups defined by clinicopathologic characteristics of breast cancer. In addition, all breast cancer cases were confirmed using medical records and pathology reports were centrally adjudicated. Other strengths include the use of standardized procedures to collect risk factor information, limited loss to follow-up, and a low proportion of missing data for most variables. However, some of the risk factor information was self-reported, and thus, recall and reporting bias may have led to measurement error. Furthermore, our study focused on recreational physical activity and did not take into account other measures of physical activity, including household and occupational activities; thus, potentially contributing to misclassification of physical activity level. Another limitation of the study is the fact the HLI score is not validated. However, this score was created on the basis of existing scientific knowledge and well-recognized public health recommendations. Furthermore, the findings of the studies using the HLI score, so far, are consistent with those from studies based on the WCRF/AICR guidelines. Self-reporting of cancer diagnosis by the subjects in the first stage of outcome ascertainment is another limitation of this study. Specifically, it is possible that some cancer cases were missed, as this method is dependent on a subject's willingness to report their diagnosis. Finally, there was also only a small proportion of women from minority groups such as Hispanic and Asian women.

Overall, this large prospective study strongly supports the view that an overall healthy lifestyle may be associated with reduced risk of breast cancer among postmenopausal women. However, additional studies should be conducted to confirm our results, as this will provide further insight into the etiology of breast cancer and will be useful in the development of primary prevention strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R. Arthur, J.E. Manson, T. Rohan
Development of methodology: R. Arthur, L. Qi, T. Rohan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Wassertheil-Smoller, J.E. Manson, L. Snetselaar, B. Caan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Arthur, B. Caan, L. Qi, T. Rohan
Writing, review, and/or revision of the manuscript: R. Arthur, S. Wassertheil-Smoller, J.E. Manson, J. Luo, L. Snetselaar, T. Hastert, L. Qi, T. Rohan
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