Published in final edited form as:

Breast Cancer Res Treat. 2018 August ; 170(3): 613–622. doi:10.1007/s10549-018-4784-0.

An estrogen-related lifestyle score is associated with risk of postmenopausal breast cancer in the PLCO cohort

Mark A. Guinter[1,2], **Alexander C. McLain**[1], **Anwar T. Merchant**[1], **Dale P. Sandler**[3], and **Susan E. Steck**[1,2]

[1]Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC

[2]Cancer Prevention and Control Program, Arnold School of Public Health, University of South Carolina, Columbia, SC

[3]Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC

Abstract

Purpose—Healthy or unhealthy lifestyle behaviors are often adopted together. We aimed to investigate the combined effect of estrogen-related lifestyle factors on postmenopausal breast cancer risk.

Methods—Data from 27,153 women enrolled in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial were used. We created an estrogen-related lifestyle score (ERLS) by incorporating a previously developed measure of estrogenic diet, alcohol intake, body mass index (BMI), and physical activity. The scores ranged from 0–6 with alcohol and BMI accounting for higher weights than the other factors. To evaluate the preventive possibilities of a low estrogen-related lifestyle and to be consistent with other published lifestyle scores, higher scores were set to correspond with potentially lower estrogenic lifestyle. The association between the ERLS and incident breast cancer was examined using Cox proportional hazards models.

Results—Participants with an ERLS of 4 or ≥5 had a 23% (HR: 0.77; 95%CI: 0.67–0.89) and 34% (HR: 0.66; 95%CI: 0.56–0.78) lower risk of breast cancer, respectively, compared to those with an ERLS ≤2 after multivariable adjustment. Estimates were similar when restricting to invasive cases or estrogen receptor positive subtypes. No single lifestyle component appeared to drive the association.

Conclusions—Our findings suggest that the combined effect of a lifestyle characterized by a low estrogenic diet, low alcohol consumption, low body weight, and high levels of physical activity are associated with a reduction in postmenopausal breast cancer risk, possibly through an influence on estrogen metabolism.

Keywords

breast cancer; lifestyle score; estrogen metabolism; behavior; epidemiology; prospective cohort study

Corresponding author: Susan Steck, 915 Greene St, Columbia, SC 29208, ssteck@sc.edu, (803) 777-1527.

The authors do not declare any conflicts of interest.

In the US, an estimated 250,000 incident breast cancer cases will be diagnosed in 2017, accounting for approximately 30% of cancer diagnoses in women, with the majority of cases occurring in postmenopausal women [1,2]. Although many well-established risk factors for postmenopausal breast cancer have been identified, not all represent opportunities for primary prevention to lessen this burden.

There is evidence linking several lifestyle factors to the development of postmenopausal breast cancer [2,3]. Both sides of the energy balance equation – excess intake in the form of adiposity and greater energy expenditure in the form of physical activity (PA) – show evidence of a positive and negative association with breast cancer, respectively [2,4]. Consumption of alcohol increases breast cancer risk [2,4]. Although evidence of a dietary association with breast cancer is less robust, it is still suggestive [5,6]. Lifestyle factors often cluster together in individuals who adopt healthy or unhealthy lifestyles, so it can be advantageous to use a combined lifestyle score to quantify how much risk can be reduced, if any, through embracing a healthy lifestyle [7]. Several studies have used indices to assess lifestyle factors as one aggregate score and have consistently reported moderate inverse associations between a healthy lifestyle and breast cancer [8–15]. Previous indices were based on adherence to cancer prevention guidelines [8,11], included behaviors specific to a study population [9], or were simply based on what is thought to constitute healthy behaviors [10,12].

Consideration of a disease mechanism in the development of a lifestyle score may help elucidate stronger associations than previous studies. In the case of postmenopausal breast cancer, the influence of estrogen exposure on mammary carcinogenesis is well-documented [16]. Regarding modifiable behaviors, increased adiposity after menopause and consumption of alcohol are positively associated with estrogen [17], whereas PA is inversely associated with estrogen [18]. Recent dietary patterns developed to correlate with estrogen levels were subsequently associated with postmenopausal breast cancer risk in some study populations [19,20], but not all [21]. One of those patterns, the estrogen-related dietary pattern (ERDP) developed by our group, was based on an estrogen profile that is specific to breast cancer risk: high unconjugated estradiol (E2) and a low ratio of 2- to 16-hydroxylated metabolites (2/16)[20].

In the present analysis, we aimed to assess the relationship between a lifestyle score based on estrogen-related lifestyle factors and postmenopausal breast cancer risk. We created the estrogen-related lifestyle score (ERLS) using the ERDP, alcohol consumption, body mass index (BMI), and PA as scoring components, and examined associations with postmenopausal breast cancer. We hypothesized that higher ERLS scores, representative of a lower combined estrogenic effect of lifestyle factors, would be inversely associated with postmenopausal breast cancer, and that more substantial associations would be present for estrogen receptor-positive (ER+) cases, and among strata of effect modifiers associated with lower estrogen exposure.

Methods

The Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO) is an initiative of the National Cancer Institute to examine the effects of screening on various cancer endpoints. Design and implementation have been described in detail elsewhere [22]. Briefly, recruitment of 76,685 men and 78,216 women aged 55 to 74 took place at 10 different screening centers across the United States between 1993 and 2001. Women in the screening arm participated in chest x-ray, flexible sigmoidoscopy, a CA-125 blood test and transvaginal ultrasound. The current analyses used only data from women randomized to the intervention arm of the study (n=39,104) who completed a dietary questionnaire (DQX) at baseline, because participants in the control arm completed a different dietary questionnaire three years post-baseline. The study population was limited to women who completed the baseline questionnaire, had a valid DQX (between 1st and 99th percentiles of energy intake, <8 missing line items), and without a personal history of cancer (except for non-melanoma skin cancer) at baseline, bringing the sample to 28,438. Participants were further excluded if they had an extreme (<15 or >55 kg/m^2; n=74) or missing (n=179) BMI, did not have data on PA (n=112), or if they did not contribute any person-time (n=58). After excluding participants with missing covariate data (n=862) the final analytic sample comprised 27,153 participants. A subsample of women within the screening arm of PLCO had estrogen metabolite (EM) data, measured by liquid chromatography-tandem mass spectrometry assay of serum samples collected at baseline. This subsample, used in the development of the ERDP, came from a nested case-control study [23] and is comprised of 386 controls and 250 confirmed breast cancer cases who were diagnosed >2 years after blood sample donation. Seventeen women who were included in the development of the ERDP were excluded in the present analysis due to missing PA data.

Data Collection

Eligible participants filled out a risk factor questionnaire at baseline. Participants self-reported their height and weight, which was used to calculate BMI. Dietary data were collected via the DQX, a 137-item food frequency questionnaire (FFQ) designed specifically for PLCO to assess typical frequency of intake over the past year. Nutrient and food intake amounts were calculated using US dietary data and the pyramid food group servings database from the US Department of Agriculture (USDA) [24]. Separate line items were included for beer, liquor, and wine; which were used to calculate alcohol drinks per day. The DQX also contained a question on the number of hours per week spent performing vigorous PA, with the response categories of: <1, 1, 2, 3, and ≥4.

Calculation of ERLS Scoring

A summary of the ERLS scoring is portrayed in Table 1. The dietary component of the ERLS was characterized using previously described ERDP score [20]. Briefly, reduced rank regression modeling was performed to identify a dietary pattern that was associated with serum levels of unconjugated E2 and the 2/16 ratio in a nested case-control of 653 postmenopausal women. The newly developed ERDP is comprised of non-whole/refined grains, tomatoes, cruciferous vegetables, cheese, fish/shellfish high in ω-3 fatty acids, franks/luncheon meats, nuts and seeds, other vegetables, fish/shellfish low in ω-3 fatty acids,

yogurt, and coffee. Intakes of these food groups were centered and scaled, then multiplied by their corresponding model weights. The total ERDP score was calculated by summing over the weighted intakes. Higher ERDP scores are positively associated with unconjugated E2 and inversely associated with the 2/16 ratio. The dietary component of the ERLS score was based on the median ERDP score (−0.0206419) for the analytic PLCO population. Women with a score greater than or equal to the median received a 0, as those diets are hypothesized to be positively associated with estrogen metabolism and breast cancer risk. Women with an ERDP score below the median received a 1.

Scoring parameters for the remaining ERLS components are similar to those outlined in the World Cancer Research Fund (WCRF) and American Institute for Cancer Research's (AICR) Second Expert Report, and the USDA's 2015 Dietary Guidelines for Americans [3,25]. Due to the strength of evidence for associations between alcohol intake and obesity status with breast cancer risk, and evidence of an estrogenic effect [3], these variables were given a stronger weight by using a three-level variable rather than two-level variable in the scoring of the ERLS. For alcohol intake, women who abstained from drinking (0 drink/week) were scored a 2; women who consumed >0 to 7 drinks/week were scored a 1; and those who consumed >7 drinks/week were scored a 0. Women were scored a 2 if they were normal weight (BMI <25.0 kg/m^2), a 1 if overweight (BMI 25.0–29.9 kg/m^2), and 0 if obese (BMI ≥30.0 kg/m^2). For PA, women who reported >2 hours/week of vigorous PA were considered active and scored a 1, and those who reported ≤2 hours/week were scored a 0. The score for each of the four different ERLS components was summed. Women with the minimum score of 0 were hypothesized to have the largest risk profile from estrogen exposure, and those with a maximum of 6 were hypothesized to have the lowest combined risk profile from estrogen-related lifestyle factors.

Breast Cancer Ascertainment

Incident breast cancer cases through December 31, 2009 were identified through self-report via annually mailed follow-up questionnaires. Other sources of ascertainment included the National Death Index, physician reports, state cancer registries, and next of kin reports. Over 96% of PLCO cases were confirmed through hospital records [26]. In the analytic cohort, a total of 1,568 incident breast cancer cases were confirmed. A supplemental form was implemented in 2007 to capture more detailed information about the diagnosis, including estrogen receptor status. Data on ER status was available for 70% of cases. Breast cancer events of interest included total breast cancer cases (including *in situ*), invasive only cases, and ER subtypes.

Statistical Approach

Pearson correlation coefficients were used to quantify the strength of the relationship between the ERLS and EMs in the subsample of women with data on EMs. Cox proportional hazards models were applied to analyze the relationship between the ERLS and incident breast cancer events, with person-time calculated from date of completed DQX to end of follow-up or event [27]. The proportional hazards assumption was evaluated using Martingale-based residuals and was not violated by exposure variables or covariates [28]. The ERLS was grouped as follows: ≤2 (referent group), 3, 4, or ≥5. The three lowest scores

(0, 1, and 2) and the two highest scores (5 and 6) were combined into single categories due to low numbers of cases. The first category hypothetically represents lifestyles with a higher exposure to estrogen. The hazard ratio (HR) and 95% confidence intervals (CI) also were calculated for the continuous ERLS score variable, and the p-value reported as a test for trend. The linearity of the continuous ERLS was evaluated and confirmed by plotting the log-hazard rate against the continuous ERLS measure. Demographic factors of age (years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other) and study center (10 categories) were included in the multivariable-adjusted models, along with total energy intake (kcal/day) for their putative roles as confounders for breast cancer. The remaining covariates included in multivariable-adjusted models were chosen using stepwise model selection with entry/exit criteria of p=0.2. Further adjustment for PMH use (current; former; never; unknown), family history of breast cancer (yes; no; unknown), education (less than high school; high school and some college; college degree; graduate degree), BMI at age 20 (kg/m^2), bilateral oophorectomy (yes; no), parity (6 categories), and age at menopause (5 categories) was included in the multivariable models. Age at first birth, age at menarche, oral contraceptive use, smoking status, and prior hysterectomy also were considered as potential confounders but were not included after performing the stepwise model selection, as they did not improve the model. Effect modification by baseline PMH use (yes; no) and parity (nulliparous; parous) was examined in stratified results, and by including an interaction term in the model. A competing risk model assessed a differential association for the ERLS on ER+ and ER− subtypes using a Wald test for heterogeneity in the stratified Lunn-McNeil approach [29]. In secondary analyses, we evaluated associations between individual ERLS components and postmenopausal breast cancer with additional adjustment for each of the ERLS components that were not the main independent variable of interest. Additionally, to evaluate if an observed association between the ERLS and postmenopausal breast cancer was primarily influenced by a single ERLS component, we removed the components one at a time from the total ERLS score to see if the estimate of association with breast cancer changed significantly. All statistical tests were two-sided at α=0.05 and all analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

The median age at baseline was 62, with an interquartile range (IQR) of 58 to 67. After a median follow-up time of 11.5 years (IQR: 10.3 to 12.8), 1,576 incident cases of breast cancer were reported, with 1,261 of those cases being invasive and the remaining 315 cases being *in situ*. Among cases where ER status was ascertained, 1,089 were ER+ and 187 were ER−. In our subsample of participants with EM data, the ERLS was moderately correlated with unconjugated E2 (r=−0.33; p<0.01) and the 2/16 ratio (r=0.20; p<0.01). The distribution of characteristics across ERLS categories for the full analytic cohort are shown in Table 2.

In Cox models with varying levels of adjustment, participants in the highest ERLS category experienced the lowest risk of postmenopausal breast cancer compared to the lowest ERLS category (Table 3). In the multivariable-adjusted model, participants with an ERLS of 4 or ≥5 had a 23% (HR: 0.77; 95%CI: 0.67–0.89) and 34% (HR: 0.66; 95%CI: 0.56–0.78) reduction in risk of breast cancer, respectively, compared to those with an ERLS ≤2 (p-

trend<0.0001). A 1-unit increase in ERLS was associated with a 11% lower risk (HR: 0.89; 95%CI: 0.85–0.92) after adjustment. Estimates were similar for invasive cases only. When restricting to ER+ subtype, the magnitude of the inverse associations strengthened slightly for those with an ERLS of 4 (HR: 0.73, 95%: 0.62–0.87) and ERLS ≥5 (HR: 0.63; 95%CI: 0.51–0.77). No significant effect estimates were observed for ER− subtypes and results from the competing risk model indicated there was no differential association for the different ER subtypes (p=0.62). There was no evidence of effect modification by baseline PMH use ($p_{interaction}$=0.54) or parity ($p_{interaction}$=0.75) (Supplementary Table 1).

Table 4 shows results from investigations of individual ERLS scoring components. In all models, the category that was associated with a score of 0, representative of higher estrogen exposure, was the referent. A modest reduction in risk was observed in participants with score of 1 for the ERDP (HR: 0.92; 95%CI: 0.83–1.02) and for those with a score of 1 for PA (HR: 0.92; 95%CI: 0.83–1.02). Significant reductions in risk were seen among individuals with an alcohol score of 2 (HR: 0.79; 95%CI: 0.66–0.95), or 1 (HR: 0.83; 95%CI: 0.72–0.95); and for individuals with a BMI score of 2 (HR:0.72; 95%CI: 0.62–0.83), or 1 (HR: 0.88; 95%CI: 0.76–1.00). The estimates of association for the ERLS remained relatively unchanged after removing individual components one at a time (Supplementary Table 2).

Discussion

In this large prospective cohort study of postmenopausal women, our findings suggest that the combined effect of modifiable lifestyle factors, namely diet, alcohol intake, BMI, and PA, is associated with risk of postmenopausal breast cancer. Specifically, women who were consuming a diet with less estrogenic potential, less alcohol, had a lower BMI, and were engaging in more PA were at reduced risk for breast cancer compared to women with less healthy lifestyles. A 1-unit increase in the ERLS towards the direction of a lifestyle that was hypothesized to have lower estrogen exposure was associated with a 11% reduction in risk. The ERLS was moderately correlated with two EMs thought to be important indicators of breast cancer risk in a subsample of women. However, the association between ERLS and breast cancer did not differ by ER subtypes.

Considering the prominence of an estrogenic influence on the development of breast cancer, the ERLS was developed to characterize the combined effect of estrogen-related lifestyle factors. Other lifestyle components, such as smoking or breastfeeding, were omitted from the ERLS as evidence of an estrogenic disease mechanism is not substantial [30]. All individual components of the ERLS exhibited inverse associations with postmenopausal breast cancer in multivariable-adjusted models, but none of the estimates of association were larger than their combined effect in the ERLS. According to the WCRF/AICR 2017 Continuous Update Project (CUP) [4], there is strong evidence of increasing risk of postmenopausal breast cancer with body fatness (represented by BMI in the ERLS), alcohol, and PA. Furthermore, in a prior PLCO investigation, a 1-unit increase in ERDP scores was associated with a significant 9% increase in risk of developing postmenopausal breast cancer [20]. The association between ERLS and postmenopausal breast cancer remained significant, with relatively no attenuation, after individual ERLS components were removed

from the total score. These results suggest no single component of the ERLS drove the observed significant association of the total ERLS with breast cancer risk.

To the best of our knowledge, this was the first application of a lifestyle score with a focus on estrogen as the primary mechanistic pathway. Prior research on lifestyle scores and breast cancer in prospective studies have yielded similar results. An *a priori* healthy lifestyle index score (HLIS) based on diet, tobacco use, alcohol, PA, and BMI reported 21% lower risk of breast cancer (HR: 0.79, 95% CI: 0.73–0.85) among the most healthy group in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort [12]. When the HLIS was applied in the same cohort, but with a dietary modification to include fish, folate, glycemic index, and other breast cancer risk-specific dietary components, the estimate of the inverse association was slightly stronger (HR: 0.74; 95% CI: 0.66–0.83) [10]. The association was strongest for ER−/progesterone receptor (PR)− breast cancer (HR: 0.60; 95% CI: 0.40–0.90), but also significant for ER+/PR+ (HR: 0.81; 95% CI: 0.67–0.98), suggesting non-estrogenic disease pathways may have played a role [10]. Also using data from EPIC, a lifestyle score was developed to evaluate conformity to the WCRF/AICR recommendations on body fatness, PA, energy dense foods and drinks, plant foods, animal foods, alcohol use, and breastfeeding. Compared to the lowest scores, all categories showed a significant inverse association with breast cancer, with the strongest association in those with greatest conformity to the prevention guidelines (HR: 0.84; 95% CI: 0.78–0.90) [8]. Conformity to WCRF/AICR recommendations has exhibited inverse associations with breast cancer risk in other populations [13–15], as well, including the Iowa Women's Health Study where associations did not differ in the presence of non-modifiable risk factors for breast cancer [14].

Evidence from case-control studies have shown similar, but stronger associations. In a case-control study of Mexican women, those in the highest quintile of a healthy index comprised of diet, PA, alcohol consumption, and tobacco smoking had 80% lower odds of developing postmenopausal breast cancer compared to the lowest quintile (odds ratio (OR): 0.20; 95% CI: 0.11–0.37) [9]. Increasing scores for a lifestyle score focused on limiting red meat, cream, and cheese; consuming more white meat, fish, fruit and vegetables; lower alcohol consumption; not smoking; higher PA; lower BMI; and longer cumulative duration of breastfeeding was associated with a reduction in risk among indigenous New Zealanders (OR: 0.47; 95% CI: 0.23–0.94), but not among non-indigenous participants (OR: 0.86; 95% CI: 0.67–1.11) [11]. Cases and controls may differentially report their behaviors in case-control studies, introducing the potential for recall bias which is a limitation when interpreting these results. The misclassification resulting from recall bias may explain why larger associations were observed among case-control studies compared to prospective cohorts for investigations of lifestyle scores and breast cancer.

There is evidence that high levels of circulating unconjugated E2 and a low 2/16 ratio may be representative of an estrogen profile that increases the risk of postmenopausal breast cancer [31]. In our subsample of women with EM data, the ERLS was inversely and positively correlated with unconjugated E2 and the 2/16 ratio, respectively. Additionally, each component of the ERLS has been associated with estrogen metabolism [17,18,20]. Therefore, it is plausible that the combined effect of these lifestyle behaviors on

postmenopausal breast cancer risk works through an influence on estrogen metabolism. Dietary behaviors are known to influence the intestinal microbiota [32], which can subsequently influence excretion or reabsorption of active estrogens [33]. Alcohol consumption may increase aromatase activity, promoting the conversion of testosterone into estrogen [34]. Adipose tissue is the largest source of endogenous estrogen in postmenopausal women [2], and there is strong evidence for a positive linear association between adipose tissue and estrogen levels in postmenopausal women [35]. The inverse association between PA and estrogen may be a result of reducing adipose-derived estrogen, or possibly through increased levels of SHBG, limiting the amount of available estrogen in active tissues [4,36].

It also is possible that the observed inverse association between the ERLS and postmenopausal breast cancer was mediated through an influence on inflammatory mechanisms. Many components of the ERDP, such as coffee, vegetables, fiber, and animal products have been shown to exhibit either inverse or positive associations with inflammatory markers [37,38]. Furthermore, the remaining components of the ERLS (BMI, alcohol, and PA) have been shown to influence systemic inflammation [39,40].

Some limitations should be considered. There is the potential for bias due to the selection of subjects, loss to follow-up, and measurement error. Although FFQs may not generate accurate estimates for absolute intakes of nutrients, they are useful for ranking individuals, and only food or food groups (not nutrients) intakes were utilized in this study [41]. The use of BMI is an imperfect proxy for adiposity, and BMI values were derived from self-reported height and weight. However, a validation study in a similar U.S. population showed strong correlation between self-reported and measured weight [42]. Our ability to detect an association for ER− cases was limited due to low numbers, however, this was not an issue for ER+ cases. A limitation for the PLCO study population is the lack of racial/ethnic diversity. However, non-Hispanic White women experience the highest incidence of breast cancer in the US, so results are generalizable to this high-risk group. We were unable to evaluate the construct validity of the ERLS in an external study population by examining its association with EMs, however, the ERLS was significantly correlated with EMs in a subsample of 636 PLCO women with EM data.

There are many strengths to our analysis, as well. The use of a large, prospective cancer cohort provided adequate power to detect small associations with information on known risk factors to appropriately adjust for confounders. The inclusion of the ERDP and pre-identification of a plausible mechanistic pathway aided in making meaningful interpretations of our results. This was a novel approach to developing a lifestyle score that is disease- and mechanism-specific.

In conclusion, our findings suggest that modifiable lifestyle behaviors have a combined effect on postmenopausal breast cancer risk, possibly through an alteration of estrogen metabolism. A lifestyle that is characterized by consumption of a diet with low estrogenic potential, low alcohol consumption, a low BMI, and high levels of PA may help to lower the risk of developing breast cancer in postmenopausal women. A collective change in lifestyle is likely more influential than focusing on specific behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was made possible in part by Grant Number T32-GM081740 from NIH-NIGMS. DPS is supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01 ES-044005l). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIGMS or NIH.

Abbreviations

2/16	Ratio of 2- to 16-hydroxylated estrogen metabolites
AICR	American Institute for Cancer Research
BMI	Body mass index
CI	Confidence interval
CUP	Continuous Update Project
DQX	Dietary questionnaire
E2	Estradiol
EM	Estrogen metabolites
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Estrogen receptor
ERDP	Estrogen related dietary pattern
ERLS	Estrogen related lifestyle score
HR	Hazard ratio
OR	Odds ratio
PA	Physical activity
PMH	Postmenopausal hormone
PR	Progesterone receptor
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
SD	Standard deviation
USDA	United States Department of Agriculture
WCRF	World Cancer Research Fund

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017; 67:7–30. DOI: 10.3322/caac.21387 [PubMed: 28055103]
2. American Cancer Society. Breast Cancer Facts & Figures 2015–2016. Atlanta: 2015.
3. World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: 2007.
4. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Breast Cancer. 2017
5. Brennan SF, Cantwell MM, Cardwell CR, Velentzis LS, Woodside JV. Dietary patterns and breast cancer risk: a systematic review and meta-analysis. Am J Clin Nutr. 2010; 91:1294–302. DOI: 10.3945/ajcn.2009.28796 [PubMed: 20219961]
6. Mourouti N, Kontogianni MD, Papavagelis C, Panagiotakos DB. Diet and breast cancer: a systematic review. Int J Food Sci Nutr. 2015; 66:1–42. DOI: 10.3109/09637486.2014.950207 [PubMed: 25198160]
7. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary Prevention of Coronary Heart Disease in Women through Diet and Lifestyle. N Engl J Med. 2000; 343:16–22. DOI: 10.1056/NEJM200007063430103 [PubMed: 10882764]
8. Romaguera D, Vergnaud A-C, Peeters PH, van Gils CH, Chan DS, Ferrari P, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr. 2012; 96:150–63. DOI: 10.3945/ajcn.111.031674 [PubMed: 22592101]
9. Sánchez-Zamorano LM, Flores-Luna L, Ángeles-Llerenas A, Romieu I, Lazcano-Ponce E, Miranda-Hernández H, et al. Healthy Lifestyle on the Risk of Breast Cancer. Cancer Epidemiol Prev Biomarkers. 2011; 20(5):912–22.
10. McKenzie F, Ferrari P, Freisling H, Chajès V, Rinaldi S, de Batlle J, et al. Healthy lifestyle and risk of breast cancer among postmenopausal women in the European Prospective Investigation into Cancer and Nutrition cohort study. Int J Cancer. 2015; 136:2640–8. DOI: 10.1002/ijc.29315 [PubMed: 25379993]
11. McKenzie F, Ellison-Loschmann L, Jeffreys M, Firestone R, Pearce N, Romieu I. Healthy lifestyle and risk of breast cancer for indigenous and non-indigenous women in New Zealand: a case control study. BMC Cancer. 2014; 14:12.doi: 10.1186/1471-2407-14-12 [PubMed: 24410858]
12. McKenzie F, Biessy C, Ferrari P, Freisling H, Rinaldi S, Chajès V, et al. Healthy Lifestyle and Risk of Cancer in the European Prospective Investigation Into Cancer and Nutrition Cohort Study. Medicine (Baltimore). 2016; 95:e2850.doi: 10.1097/MD.0000000000002850 [PubMed: 27100409]
13. Romaguera D, Gracia-Lavedan E, Molinuevo A, de Batlle J, Mendez M, Moreno V, et al. Adherence to nutrition-based cancer prevention guidelines and breast, prostate and colorectal cancer risk in the MCC-Spain case-control study. Int J Cancer. 2017; 141:83–93. DOI: 10.1002/ijc.30722 [PubMed: 28380695]
14. Nomura SJO, Inoue-Choi M, Lazovich D, Robien K. WCRF/AICR recommendation adherence and breast cancer incidence among postmenopausal women with and without non-modifiable risk factors. Int J Cancer. 2016; 138:2602–15. DOI: 10.1002/ijc.29994 [PubMed: 26756307]
15. Harris HR, Bergkvist L, Wolk A. Adherence to the World Cancer Research Fund/American Institute for Cancer Research recommendations and breast cancer risk. Int J Cancer. 2016; 138:2657–64. DOI: 10.1002/ijc.30015 [PubMed: 26804371]
16. Samavat H, Kurzer MS. Estrogen metabolism and breast cancer. Cancer Lett. 2015; 356:231–43. DOI: 10.1016/j.canlet.2014.04.018 [PubMed: 24784887]
17. Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer MJ, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst. 1995; 87:1297–302. DOI: 10.1093/JNCI/87.17.1297 [PubMed: 7658481]
18. Choudhury F, Bernstein L, Hodis HN, Stanczyk FZ, Mack WJ. Physical activity and sex hormone levels in estradiol- and placebo-treated postmenopausal women. Menopause. 2011; 18:1079–86. DOI: 10.1097/gme.0b013e318215f7bd [PubMed: 21646925]

19. Harris HR, Bergkvist L, Wolk A. An estrogen-associated dietary pattern and breast cancer risk in the Swedish Mammography Cohort. Int J Cancer. 2015; 137:2149–54. DOI: 10.1002/ijc.29586 [PubMed: 25924604]
20. Guinter MA, McLain AC, Merchant AT, Sandler DP, Steck SE. A dietary pattern based on estrogen metabolism is associated with breast cancer risk in a prospective cohort of postmenopausal women. Int J Cancer. 2018; [published Online First: 2018 March 15]. doi: 10.1002/ijc.31387
21. Fung TT, Schulze MB, Hu FB, Hankinson SE, Holmes MD. A dietary pattern derived to correlate with estrogens and risk of postmenopausal breast cancer. Breast Cancer Res Treat. 2012; 132:1157–62. DOI: 10.1007/s10549-011-1942-z [PubMed: 22218885]
22. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials. 2000; 21:273S–309S. [PubMed: 11189684]
23. Fuhrman BJ, Schairer C, Gail MH, Boyd-Morin J, Xu X, Sue LY, et al. Estrogen metabolism and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2012; 104:326–39. DOI: 10.1093/jnci/djr531 [PubMed: 22232133]
24. Tippett, Katherine S., Cypel, Yasmin S. Design and Operation: The Continuing Survey of Food Intakes by Individuals and the Diet and Health Knowledge Survey, 1994-96. US Dep Agric Agric Res Serv Nationwide Food Surv Rep; 1997. p. 96-96.
25. 2015-2020 Dietary Guidelines for Americans. 8th. Washington, D.C.: 2015.
26. Hayes RB, Sigurdson A, Moore L, Peters U, Huang W-Y, Pinsky P, et al. Methods for etiologic and early marker investigations in the PLCO trial. Mutat Res. 2005; 592:147–54. DOI: 10.1016/j.mrfmmm.2005.06.013 [PubMed: 16054167]
27. Cox DR. Regression Models and Life-Tables. J R Stat Soc Ser B. 1972; 34:187–220. DOI: 10.2307/2985181
28. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika. 1982; 69:239–41. DOI: 10.1093/biomet/69.1.239
29. Lunn M, McNeil D. Applying Cox Regression to Competing Risks. Biometrics. 1995; 51:524.doi: 10.2307/2532940 [PubMed: 7662841]
30. Hulka BS, Moorman PG. Breast cancer: hormones and other risk factors. Maturitas. 2001; 38:103–13-6. [PubMed: 11311599]
31. Ziegler RG, Fuhrman BJ, Moore SC, Matthews CE. Epidemiologic studies of estrogen metabolism and breast cancer. Steroids. 2015; 99:67–75. DOI: 10.1016/j.steroids.2015.02.015 [PubMed: 25725255]
32. Albenberg LG, Wu GD. Diet and the Intestinal Microbiome: Associations, Functions, and Implications for Health and Disease. Gastroenterology. 2014; 146:1564–72. DOI: 10.1053/j.gastro.2014.01.058 [PubMed: 24503132]
33. Shapira I, Sultan K, Lee A, Taioli E. Evolving Concepts: How Diet and the Intestinal Microbiome Act as Modulators of Breast Malignancy. ISRN Oncol. 2013; 2013:1–10. DOI: 10.1155/2013/693920
34. Gavaler JS, Van Thiel DH. The association between moderate alcoholic beverage consumption and serum estradiol and testosterone levels in normal postmenopausal women: relationship to the literature. Alcohol Clin Exp Res. 1992; 16:87–92. [PubMed: 1558307]
35. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev. 2004; 5:153–65. DOI: 10.1111/j.1467-789X.2004.00142.x [PubMed: 15245384]
36. Schmidt S, Monk JM, Robinson LE, Mourtzakis M. The integrative role of leptin, oestrogen and the insulin family in obesity-associated breast cancer: potential effects of exercise. Obes Rev. 2015; 16:473–87. DOI: 10.1111/obr.12281 [PubMed: 25875578]
37. Calder PC, Ahluwalia N, Brouns F, Buetler T, Clement K, Cunningham K, et al. Dietary factors and low-grade inflammation in relation to overweight and obesity. Br J Nutr. 2011; 106(Suppl):S5–78. DOI: 10.1017/s0007114511005460 [PubMed: 22133051]
38. Barbaresko J, Koch M, Schulze MB, Nothlings U. Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review. Nutr Rev. 2013; 71:511–27. DOI: 10.1111/nure.12035 [PubMed: 23865797]

39. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr. 2006; 83:461S–465S. [PubMed: 16470013]

40. O'Connor M-F, Irwin MR. Links Between Behavioral Factors and Inflammation. Clin Pharmacol Ther. 2010; 87:479–82. DOI: 10.1038/clpt.2009.255 [PubMed: 20130566]

41. Willett, W. Nutritional Epidemiology. Oxford University Press; 2012.

42. Lin CJ, DeRoo LA, Jacobs SR, Sandler DP. Accuracy and reliability of self-reported weight and height in the Sister Study. Public Health Nutr. 2012; 15:989–99. DOI: 10.1017/S1368980011003193 [PubMed: 22152926]

Table 1

Scoring parameters for estrogen-related lifestyle score (ERLS)

ERLS factor	Score	Description
ERDP	0	≥ median ERDP score
	1	< median ERDP score
Alcohol use	0	Heavy: >7 drinks/week
	1	Moderate: >0 to 7 drinks/week
	2	Abstainer: 0 drinks/week
Weight Status	0	Obese: BMI ≥30 kg/m^2
	1	Overweight: BMI 25.0–29.9 kg/m^2
	2	Normal weight: BMI <25 kg/m^2
Physical Activity (PA)	0	Inactive: ≤2 hours/week of vigorous PA
	1	Active: >2 hours/week of vigorous PA

BMI: body mass index; ERDP: estrogen related dietary pattern; ERLS: estrogen related lifestyle score; PA: physical activity

Table 2

Population characteristics across estrogen related lifestyle score (ERLS) categories

	ERLS			
	<2 (high estrogenic potential)	**3**	**4**	**>5 (low estrogenic potential)**
n	7,469	7,565	7,345	4,774
Breast cancer cases				
Total (%)	459 (6.1)	491 (6.5)	400 (5.4)	226 (4.7)
Invasive (%)	368 (4.9)	401 (5.3)	308 (4.2)	184 (3.9)
ER+ (%)	321 (4.3)	342 (4.5)	272 (3.7)	154 (3.2)
ER− (%)	56 (0.7)	56 (0.7)	48 (0.7)	27 (0.6)
ERDP score (mean (95%CI))	0.31 (0.30, 0.33)	0.05 (0.04, 0.07)	−0.14 (−0.15, −0.13)	−0.39 (−0.40, −0.37)
(ERLS: 0) ≥ median, %	78.6	56.8	38.6	12.0
(ERLS: 1) < median, %	21.4	43.2	61.4	88.0
Alcohol (drinks/week, mean (95%CI))	4.1 (3.9, 4.3)	3.4 (3.2, 3.5)	2.3 (2.2, 2.4)	0.8 (0.7, 0.8)
(ERLS: 0) >7, %	22.2	17.2	9.5	0.0
(ERLS: 1) >0–7, %	69.4	65.6	69.1	53.1
(ERLS: 2) 0, %	8.4	17.2	21.4	46.9
BMI (kg/m^2, mean (95%CI))	31.9 (31.8, 32.0)	27.3 (27.2, 27.4)	24.6 (24.5, 24.7)	23.0 (22.9, 23.1)
(ERLS: 0) ≥30, %	64.3	20.5	3.6	0.0
(ERLS: 1) 25.0–29.9, %	31.5	50.9	37.6	11.6
(ERLS: 2) <25, %	4.2	28.6	58.8	88.4
Hours of vigorous PA per week (%)				
(ERLS: 0) ≤2	81.1	51.4	28.6	8.8
(ERLS: 1) >2	18.9	48.6	71.4	91.2
Age (years, mean (95%CI))	61.9 (61.7, 62.0)	62.4 (62.3, 62.5)	62.7 (62.6, 62.9)	63.0 (62.9, 63.2)
Total energy intake (kcal/day, mean (95%CI))	1,894 (1880, 1909)	1,763 (1750, 1777)	1,677 (1664, 1690)	1,577 (1562, 1592)
BMI at age 20 (kg/m^2, mean (95%CI))	22.3 (22.2, 22.4)	21.3 (21.2, 21.4)	20.7 (20.7, 20.8)	20.4 (20.4, 20.5)
PMH status (%)				
Current	45.4	51.7	54.3	57.2
Former	17.8	15.9	15.4	14.8
Never	36.2	32.1	29.8	27.7
Unknown	0.6	0.3	0.5	0.3
Race (%)				
White, Non-Hispanic	92.3	91.8	91.4	89.3
Black, Non-Hispanic	5.2	4.7	3.3	2.4
Hispanic	1.2	1.2	1.2	1.1
Asian	0.6	1.8	3.5	6.8
Other	0.7	0.5	0.6	0.4
Smoking (%)				
Current	9.5	9.8	8.2	6.7
Former	37.7	34.5	33.3	28.3

	ERLS			
	<2 (high estrogenic potential)	**3**	**4**	**>5 (low estrogenic potential)**
Never	52.8	55.7	58.5	65.0
Education (%)				
< HS	6.7	6.1	4.7	4.6
HS grad and some college	68.2	64.0	62.3	61.7
College grad	13.5	15.8	17.4	16.6
Postgraduate	11.6	14.1	15.6	17.1
Live births (%)				
None	6.6	7.6	7.6	7.8
1	6.9	7.3	7.1	7.3
2	21.7	23.3	25.5	26.3
3	25.7	25.3	26.1	26.2
≥ 4	39.1	36.5	33.7	32.4
Age at menopause (%)				
< 40	15.3	13.5	12.6	12.9
40–44	14.1	14.0	13.4	14.3
45–59	22.7	23.1	23.4	25.3
50–54	36.4	37.8	38.9	36.8
≥55	11.5	11.6	11.7	10.7
Bilateral oophorectomy (%)				
No	88.0	88.9	89.7	89.2
Yes	12.0	11.1	10.3	10.8
Family history of breast cancer (%)				
No	84.3	84.7	85.4	85.2
Yes	14.5	14.4	13.7	14.0
Unknown	1.2	1.0	0.9	0.9

BMI: body mass index; CI: confidence interval; ER: estrogen receptor; ERDP: estrogen related dietary pattern; ERLS: estrogen related lifestyle score; HS: high school; PA: physical activity; PMH: postmenopausal hormone; SD: standard deviation

Table 3

Hazard ratios (95% CI) for the relationship between estrogen related lifestyle score (ERLS) and postmenopausal breast cancer

	ERLS				
	≤2 (high estrogenic potential)	3	4	≥5 (low estrogenic potential)	Estimate for continuous ERLS,[a] p-trend
Total breast cancer					
No. of cases	459	491	400	226	
Age-adjusted	1.00 (ref)	1.05 (0.92, 1.19)	0.87 (0.76, 0.99)	0.75 (0.64, 0.88)	0.92 (0.89, 0.96) p<0.0001
Age- and TEI-adjusted	1.00 (ref)	1.02 (0.90, 1.16)	0.84 (0.73, 0.96)	0.72 (0.61, 0.84)	0.91 (0.88, 0.95) p<0.0001
Multivariable-adjusted[b]	1.00 (ref)	0.97 (0.85, 1.11)	0.77 (0.67, 0.89)	0.66 (0.56, 0.78)	0.89 (0.85, 0.92) p<0.0001
Invasive					
No. of cases	368	401	308	184	
Age-adjusted	1.00 (ref)	1.07 (0.92, 1.23)	0.83 (0.72, 0.97)	0.76 (0.64, 0.91)	0.92 (0.88, 0.96) p=0.0003
Age- and TEI -adjusted	1.00 (ref)	1.05 (0.91, 1.21)	0.81 (0.69, 0.94)	0.73 (0.61, 0.88)	0.91 (0.87, 0.95) p<0.0001
Multivariable-adjusted[b]	1.00 (ref)	0.99 (0.86, 1.15)	0.74 (0.63, 0.87)	0.67 (0.56, 0.82)	0.89 (0.85, 0.93) p<0.0001
ER+					
No. of cases	321	342	272	154	
Age-adjusted	1.00 (ref)	1.04 (0.89, 1.21)	0.84 (0.71, 0.98)	0.73 (0.60, 0.88)	0.91 (0.87, 0.96) p=0.0001
Age- and TEI -adjusted	1.00 (ref)	1.01 (0.87, 1.18)	0.81 (0.69, 0.95)	0.70 (0.57, 0.84)	0.90 (0.86, 0.94) p<0.0001
Multivariable-adjusted[b]	1.00 (ref)	0.96 (0.82, 1.12)	0.73 (0.62, 0.87)	0.63 (0.51, 0.77)	0.87 (0.83, 0.92) p<0.0001
ER−					
No. of cases	56	56	48	27	
Age-adjusted	1.00 (ref)	1.04 (0.72, 1.52)	0.91 (0.61, 1.34)	0.79 (0.50, 1.26)	0.95 (0.84, 1.06) p=0.34
Age- and TEI-adjusted	1.00 (ref)	1.04 (0.71, 1.51)	0.90 (0.61, 1.34)	0.78 (0.49, 1.25)	0.94 (0.84, 1.06) p=0.32
Multivariable-adjusted[b]	1.00 (ref)	1.04 (0.71, 1.53)	0.92 (0.61, 1.38)	0.84 (0.52, 1.37)	0.96 (0.85, 1.09) p=0.52

CI: confidence interval; ER: estrogen receptor; ERLS: estrogen related lifestyle score; PMH: postmenopausal hormone; TEI: total energy intake

[a] HR corresponds to 1-unit increase in ERLS score.

[b] Includes adjustment for age, TEI, PMH, education, BMI at age 20, bilateral oophorectomy, parity, age at menopause, family history of breast cancer, race/ethnicity, and study center.

Table 4

Hazard ratios (95% CI) for the relationship between the individual estrogen related lifestyle score (ERLS) components and postmenopausal breast cancer

	No. of cases (%)[a]	Age-adjusted	Age- and TEI -adjusted	Multivariable-adjusted[b]
ERDP score				
≥ median	827 (6.1)	1.00 (ref)	1.00 (ref)	1.00 (ref)
< median	749 (5.5)	0.91 (0.82, 1.00)	0.90 (0.82, 1.00)	0.92 (0.83, 1.02)
Alcohol (drinks/week)				
>7	264 (7.3)	1.00 (ref)	1.00 (ref)	1.00 (ref)
>0 to 7	1,025 (5.8)	0.79 (0.69, 0.91)	0.80 (0.70, 0.92)	0.83 (0.72, 0.95)
0	287 (5.0)	0.71 (0.60, 0.84)	0.71 (0.60, 0.84)	0.79 (0.66, 0.95)
BMI (kg/m^2)				
≥30	388 (5.9)	1.00 (ref)	1.00 (ref)	1.00 (ref)
25.0 to 29.9	578 (6.1)	1.00 (0.88, 1.13)	0.97 (0.85, 1.10)	0.88 (0.76, 1.00)
<25	610 (5.5)	0.90 (0.80, 1.03)	0.86 (0.76, 0.98)	0.72 (0.62, 0.83)
Hours of vigorous PA per week				
≤2	733 (5.9)	1.00 (ref)	1.00 (ref)	1.00 (ref)
>2	843 (5.7)	0.95 (0.86, 1.05)	0.93 (0.84, 1.03)	0.92 (0.83, 1.02)

BMI: body mass index; CI: confidence interval; ERDP: estrogen related dietary pattern; ERLS: estrogen related lifestyle score; PA: physical activity; PMH: postmenopausal hormone; TEI: total energy intake

[a] Percentage indicates proportion of cases that occurred among participants within each ERLS component strata.

[b] Includes adjustment for each other ERLS component that is not the main predictor, age, TEI, PMH, education, BMI at age 20, bilateral oophorectomy, parity, age at menopause, family history of breast cancer, race/ethnicity, and study center.