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A dietary pattern based on estrogen metabolism is associated with breast cancer risk in a prospective cohort of postmenopausal women

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Abstract

Increased exposure to estrogen is a risk factor for postmenopausal breast cancer, and dietary factors can influence estrogen metabolism. However, studies of diet and breast cancer have been inconclusive. We developed a dietary pattern associated with levels of unconjugated estradiol and the ratio of 2- and 16-hydroxylated estrogen metabolites in a subsample of Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO) participants (n=653) using reduced rank regression, and examined its association with postmenopausal breast cancer prospectively in the larger PLCO cohort (n=27,488). The estrogen-related dietary pattern (ERDP) was comprised of foods with positively-weighted intakes (non-whole/refined grains, tomatoes, cruciferous vegetables, cheese, fish/shellfish high in ω-3 fatty acids, franks/luncheon meats) and negatively-weighted intakes (nuts/seeds, other vegetables, fish/shellfish low in ω-3 fatty acids, yogurt, coffee). A 1-unit increase in the ERDP score was associated with an increase in total (HR:1.09, 95%CI:1.01-1.18), invasive (HR:1.13; 95%CI:1.04-1.24) and estrogen receptor (ER)-positive (HR: 1.13, 95%CI:1.02-1.24) breast cancer risk after adjustment for confounders. Associations were observed for the fourth quartile of ERDP compared to the first quartile for overall breast cancer (HR:1.14; 95% CI:0.98-1.32), invasive cases (HR:1.20, 95%CI:1.02-1.42) and ER-positive cases (HR:1.19; 95%CI:0.99-1.41). The increased risk associated with increasing ERDP score was more apparent in strata of some effect modifiers (postmenopausal hormone therapy non-users and non-obese participants) where the relative estrogen exposure due to that factor was lowest, although the p-values for interaction were not statistically significant. Results suggest a dietary pattern based on estrogen metabolism is positively associated with postmenopausal breast cancer risk, possibly through an estrogenic influence.

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Keywords

breast cancer; dietary pattern; estrogen metabolism; reduced rank regression

Breast cancer, the most commonly diagnosed cancer among women worldwide, is a disease of strong hormonal influence.[1] Serum and urinary levels of estrogen metabolites (EMs) have consistently been associated with postmenopausal breast cancer risk in prospective studies.[2] Therefore, modifiable lifestyle risk factors for postmenopausal breast cancer that are associated with estrogen metabolism may present opportunities for primary prevention.

Diet is commonly studied as a point of intervention for reducing cancer risk, however there have been conflicting results in dietary investigations into breast cancer risk, with the exception of alcohol which is considered an established risk factor.[3,4] It is likely that the practice of studying dietary components in isolation may contribute to the inconclusive findings for associations with breast cancer, as it does not take into account the interactions between nutrients and phytochemicals.[5] Therefore, it is beneficial to study diet in its entirety using dietary pattern analyses when investigating a potential association with breast cancer. Emerging evidence has supported an association between some dietary patterns and incident breast cancer risk.[4,6] Many of the diets that have indicated an inverse relationship with breast cancer are characterized by high intakes of fruits and vegetables, and diets with increased risk typically have higher intakes of fat and animal products.[4,7,8]

In order to address some of the inconclusive findings in the literature on diet and breast cancer, it may be advantageous to consider the mechanistic pathway by which a potential association may occur. Nutritional factors can influence many hormonal processes in women, such as the development of breasts, and the onset of both menarche and menopause.[9,10] Therefore, diet may have a role in altering estrogen metabolism and subsequently breast cancer risk, although data on the relationship between diet and estrogen metabolism is scarce. A relatively new approach to dietary pattern analyses, reduced rank regression (RRR), allows for the use biomarkers, such as EMs, in developing a dietary pattern that can then be investigated in association with disease endpoints.[11] Previously, Fung et al. developed a dietary pattern correlated with serum levels of estradiol and estrone sulfate using RRR, but the pattern subsequently was not associated with breast cancer among postmenopausal women in the Nurses'lth Study (NHS).[12] However, application of the same estrogen-correlated dietary pattern in a Swedish cohort identified a positive association with incident breast cancer.[6]

In the present analysis, we used RRR to develop a dietary pattern that is associated with EMs that are hypothesized to be associated with breast cancer risk. Using the liquid chromatography-tandem mass spectrometry assay (LC/MS-MS), 15 EMs can be measured in an accurate and reproducible method with enough sensitivity to detect the low levels present in postmenopausal women.[13] Measurement of the parent estrogens'nstream EMs allows for ratios of competing metabolic pathways to be quantified. There is evidence that 2-hydroxylation of the parent estrogens is inversely associated, and 16-hydroxylation is positively associated with postmenopausal breast cancer.[2] Therefore, increases in the ratio of 2- to 16-hydroxylated EMs (2/16) is hypothesized to indicate a beneficial shift in estrogen

metabolism with respect to breast cancer risk.[2] Based on this evidence, and established evidence linking unconjugated estradiol (E2) to postmenopausal breast cancer risk,[2,14] we used RRR to develop a dietary pattern associated with circulating E2 and 2/16 from serum samples. This newly developed estrogen related dietary pattern (ERDP) was applied in a prospective cohort of women to examine an association with total postmenopausal breast cancer and by estrogen-receptor (ER) subtype. The potential for effect modification by other estrogen-related risk factors and family history of breast cancer was examined.

Methods

Study Population

The Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO) is a large population-based trial designed to determine the effects of screening on cancer prognosis and mortality. Design and implementation has been described in detail elsewhere.[15] Briefly, 76,685 men and 78,216 women aged 55 to 74 were recruited at 10 different screening centers across the United States between 1993 and 2001. Eligible participants underwent a physical examination and filled out a questionnaire with information on demographics, medical history, family history, lifestyle factors, and recent history of participation in screening examinations at baseline. Follow-up continued for 13 years or until December 31, 2009. For the current study, only data from the women randomized to the intervention arm of the study (n=39,104) that participated in chest x-ray, flexible sigmoidoscopy and a digital rectal examination, and a CA-125 blood test and transvaginal ultrasound were used. Over 82% of participants in the screening arm completed the DQX. The population was limited to women who completed the baseline questionnaire, a valid DQX (caloric intake between 1st and 99th percentiles, <8 missing line items), and without a personal history of cancer (n=28,438). Participants were further excluded if they had an extreme body mass index (BMI) (<15 or >55 kg/m^2; n=74), if they did not contribute any person-time (n=58) or were missing covariate data (n=818), bringing the final analytic sample to 27,488.

Subsample and EM Assay

A subset of postmenopausal women randomized to the screening arm of PLCO for whom information on serum EMs was available was utilized to derive the ERDP. Complete information on the nested study has been published elsewhere.[16] Briefly, the nested study population was drawn from all 1,141 incident breast cancer cases diagnosed from the start of recruitment in 1993 through June 30, 2005, and a random sample of 1,141 control subjects. After excluding women who were not postmenopausal, were not using postmenopausal hormone therapy (PHT) at baseline, or had prior diagnoses of cancer, the sample was reduced to 390 cases and 453 controls. For the purposes of the present analysis, cases who were diagnosed <2 years after serum sample donation (n=98) were excluded to avoid the possibility of disease processes affecting estrogen levels. Women without a valid DQX (n=77) or with implausible EM levels (i.e., if they were outside of 25th and 75th percentile, plus/minus three times interquartile range; n=15) were further excluded. The final analytic sample for the RRR procedure included 393 controls and 260 confirmed cases, with a mean of 5.25 years from sample donation to breast cancer diagnosis among cases.

Serum samples from women in the subsample were collected at baseline, stored at –80°C and were thawed at 4°C. The LC/MS-MS assay was used to measure the parent estrogens along with their metabolites in the 2-, 4-, and 16-hydroxylation pathways, for a total of15 EMs. The specifics of sample preparation and LC/MS-MS methods have been described elsewhere.[17] The coefficient of variation for all EMs was <5%, with even lower coefficients evident for the parent estrogens (<3%) and E2 (<2%).[16]

Dietary Measurement

The DQX, a 137-item food frequency questionnaire, was designed specifically for PLCO and asked about typical frequency of intake over the past year. Typical portion size was assessed for 77 of the items. 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).[18] Food and nutrient values were used to create food groups based on the USDA's My Pyramid Equivalents Database (MPED), with additional groups created for cruciferous vegetables, tea, and coffee.[19] The 32 groups used in the present analysis are shown in Supplementary Table 1.

Breast Cancer Ascertainment

Incident breast cancer cases were identified primarily 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 all cases in the total PLCO cohort have been confirmed through hospital records.[20] In the analytic cohort, a total of 1,569 incident breast cancer cases were confirmed. Six cases ascertained from death certificates and 58 self-reported cases could not be confirmed. These cases were excluded, along with 26 erroneously reported cases. A supplemental form was implemented in 2007 to capture more detailed information about the diagnosis, including estrogen receptor status, and was available for 98% of cases in the analytic cohort. Separate models were examined for the outcomes of total breast cancer (including invasive and *in* situ cases), invasive breast cancer, and ER subtypes of total breast cancers.

Development of the ERDP

To identify foods that are correlated with serum levels of unconjugated E2 and the 2/16 ratio, RRR modeling was applied to the subsample of 653 participants with EM data. An approach using RRR determines linear functions of predictors, which in the present case are food groups, by maximizing the explained variation in multiple disease-specific response variables, comprised of E2 and the 2/16 ratio.[21] In order to ensure RRR factors are based on how much variation in the outcome they explain, all intakes were centered and scaled so that their mean ± standard deviation (SD) is equal to 0 ± 1. Only the first factor was retained for development of the ERDP because it represented a dietary pattern that explained the largest variation in the EM. Initially, all 32 food groups were entered into the model at once. Those with a variable importance in projection statistic (VIP) greater than 0.8 were retained and re-entered into the RRR model, as they represent the food groups which are the strongest contributors to RRR factors scores.[22] The model weights were extracted from the final RRR model from PROC PLS using SAS version 9.4 (SAS Inc., Cary, NC). To calculate the ERDP score in the full analytic PLCO cohort food group intakes were centered and scaled, then

multiplied by their corresponding model weights (Table 1) for each of the retained food groups. The total ERDP score was calculated by summing over the weighted intakes. This same calculation method was applied to score the ERDP for the full analytic cohort.

Statistical Analysis

Baseline comparisons of participant characteristics by ERDP quartiles were performed using t-tests and chi-square tests for continuous and categorical variables, respectively. Cox proportional hazards models were applied to prospectively analyze the relationship between ERDP scores and incident breast cancer events, with person-time contributed as a time scale variable. ERDP scores were categorized into quartiles, with the first quartile set as the referent. The first quartile hypothetically represents diets with an estrogen profile associated with the lowest breast cancer risk (low levels of unconjugated E2 and high 2/16 ratio). The hazard ratio and 95%CI also were calculated for the continuous ERDP score variable, and the p-value reported as a test for trend. Demographic factors of age (years), race/ethnicity (non-Hispanic White; non-Hispanic Black; Hispanic; Asian or other), education (< high school; high school graduate or some college; college graduate; postgraduate), and study center (10 categories) were included in the multivariable-adjusted models, along with total caloric intake (kcal/day) for their putative roles as confounders for breast cancer, as determined by directed acyclic graphs and review of the literature. The remaining covariates included in multivariable-adjusted models were chosen using stepwise model selection with entry/exit criteria of p=0.2. After use of stepwise selection for confounders, the excluded potential confounders were entered into the multivariable model individually to see if the effect estimate changed by greater than or equal to 10%, which would warrant their inclusion. Further adjustment for PHT use (current; former; never), body mass index (BMI) (kg/m^2), BMI at age 20 (kg/m^2), alcohol consumption (abstainer; 1-7; >7 drinks/week), family history of breast cancer (yes; no), bilateral oophorectomy (yes; no), parity (6 categories), age at menopause (5 categories), hours of vigorous physical activity per week (6 categories) was included. 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 or change the effect estimate by greater than or equal to 10%. The potential for effect modification by BMI (18.5-29.9 kg/m^2; ≥30 kg/m^2), baseline PHT use (yes; no), alcohol consumption (<1 drink/week; ≥1/week), parity (nulliparous; parous), vigorous physical activity per week (<2 hours; ≥2 hours), and family history of breast cancer (yes; no) was assessed using a multiplicative interaction term in the model and evaluated for statistical significance using a Wald test. All models were performed with total breast cancer, invasive breast cancer, and by ER subtype. A competing risk model was used to test for a differential effect for ER+ and ER- outcomes. All statistical tests were two-sided at α=0.05, with the exception of interaction p-values which were considered statistically significant at p<0.10.

Results

Unconjugated E2 and the 2/16 ratio were moderately and inversely correlated (r= -0.51; p<0.0001) in the subsample of 653 women. After applying the VIP criteria, 11 food groups with a VIP >0.8 were retained and re-entered into the RRR procedure. The final list of food

groups included in the ERDP is shown in Table 1. Overall, 4.9% of the total variation in both EMs was explained by the ERDP. Intakes of non-whole/refined grains, tomatoes, cruciferous vegetables, cheese, fish/shellfish high in ω-3 fatty acids, and franks/luncheon meats were added; and intakes of nuts and seeds, other vegetables, fish/shellfish low in ω-3 fatty acids, yogurt, and coffee were subtracted to calculate the ERDP score. The "other vegetables" group includes vegetables except for tomatoes, potatoes and orange, dark leafy, cruciferous, and starchy vegetables. For example, this group includes cucumber, onion, green pepper, beet, celery, and lettuce. The resulting ERDP scores were weakly but significantly correlated with unconjugated E2 ($r=0.27$; $p<0.0001$) and the 2/16 ratio ($r=-0.16$; $p<0.0001$) (Supplementary Table 2). When considering the intakes of ERDP food groups, the strongest correlates with unconjugated E2 were non-whole/refined grains ($r=.10$; $p=0.01$), cheese ($r=0.16$; $p<0.0001$), yogurt ($r=-0.10$; $p=0.01$), and franks/luncheon meats ($r=0.11$; $p=0.001$). Only intakes for non-whole/refined grains ($r=-0.09$; $p=0.02$) and cheese ($r=-0.08$; $p=0.05$) were significantly correlated with the 2/16 ratio. Increasing ERDP scores are positively correlated with unconjugated E2 and negatively correlated with the 2/16 ratio. The highest mean E2 and lowest mean 2/16 ratio were observed in the fourth ERDP quartile among participants with EM data (Supplementary Table 3).

Table 1 compares the mean intakes of included food groups across extreme quartiles of unconjugated E2 and the 2/16 ratio. On average, participants in the highest quartile of unconjugated E2 consumed higher amounts of non-whole/refined grains (4.45 vs. 3.90; $p=0.01$), cheese (0.43 vs. 0.29; $p<0.01$), and franks/luncheon meats (0.34 vs. 0.21; $p=0.01$) compared to participants in the first quartile. Mean consumption of coffee (2.30 vs. 3.09; $p=0.04$) and yogurt (0.08 vs 0.12; $p=0.03$) were significantly lower among participants in the highest quartile of unconjugated E2 compared to the first. There were no significant differences in mean intakes when comparing extreme quartiles of the 2/16 ratio.

There were 1,592 confirmed incident cases of breast cancer (n=1,248 invasive) over an average follow-up of 10.9 years. Among the cases, 1,097 were ER+ and 189 were ER-. The mean ± SD ERDP score was -0.006± 0.646 with a range of -4.515 to 6.578. Women who were diagnosed with breast cancer during follow-up had significantly higher mean ERDP scores at baseline compared to women who were not diagnosed during follow-up (0.037 vs. -0.009, respectively; $p=0.006$). Baseline characteristics for the full analytic cohort, stratified by ERDP quartiles, are shown in Table 2. There was a stepwise increase in the number of total cases from the first to fourth quartiles although the differences across quartiles was not significant ($p=0.12$). Women in the fourth quartile of the ERDP were younger, had a higher mean BMI, higher daily caloric intake, were more likely to have had a bilateral oophorectomy, and were more likely to be non-Hispanic White compared to women in the first quartile. There was no clear trend for alcohol, with a higher proportion of both abstainers and heavier drinkers in the highest quartile of ERDP. A similar pattern was seen for physical activity. There were no differences in PHT use, parity, family history of breast cancer, or age at menopause across ERDP quartiles. Participants in the highest quartile of ERDP score consumed the most non-whole/refined grains, tomatoes, cheese, and franks/luncheon meats. On the contrary, participants in the lowest quartile consumed the most coffee, nuts and seeds, fish/shellfish low in ω-3 fatty acids, yogurt, and other vegetables.

Results from the time-to-event analyses are shown in Table 3. In models using ERDP quartiles, participants in the fourth quartile were at increased risk of postmenopausal total breast cancer (HR: 1.14; 95% CI: 0.98, 1.32) and invasive breast cancer (HR: 1.20; 95%CI: 1.02, 1.42) after multivariable adjustment. All quartiles were positively associated with risk, with increasing magnitude of effect estimates with increasing quartiles, compared to the first for total (p-trend=0.04) and invasive breast cancer (p-trend=0.005). The continuous ERDP variable was positively associated with total and invasive breast cancer risk. A 1-unit increase in ERDP was associated with a 9% increase in risk (HR: 1.09; 95% CI: 1.01, 1.18) for total and 13% increase in risk for invasive (HR: 1.13; 95%CI: 1.04, 1.24) after multivariable adjustment.

The ERDP was associated with ER+ but not ER- breast cancer (Table 3). The multivariable effect estimates for continuous ERDP were 1.13 (95%CI: 1.02-1.24; p-trend=0.02) and 1.07 (95%CI: 0.85-1.35; p-trend=0.54), respectively. The competing risk model did not indicate evidence of a differential effect of the ERDP by ER subtypes (p=0.87; data not shown).

There was no evidence for effect modification by alcohol consumption and PA. However, there was some indication that PHT, BMI, parity, and family history of breast cancer may modify the effect of the ERDP (Table 4), although p-values for interaction were not significant. In stratified results, estimates of association were higher in strata of some effect modifiers where estrogen exposure is thought to be lowest (e.g., among PHT non-users, and participants with lower BMI). In the case of parity, estimates were higher in nulliparous women. An association between the ERDP and postmenopausal breast cancer was observed in women without a family history of breast cancer, but not among those with a family history.

Discussion

We developed a dietary pattern that was significantly associated with serum levels of unconjugated E2 and the 2/16 ratio in postmenopausal women. Intakes of non-whole/refined grains, cheese, franks/luncheon meats, and yogurt were most strongly correlated with the derived pattern. When applied in a prospective cohort of women, the ERDP was positively associated with total and invasive postmenopausal breast cancer risk, and the association was present in ER+ but not ER- breast cancer. The risk associated with high ERDP scores was higher within strata of some effect modifiers hypothesized to have lower exposure to estrogen. These results suggest that women who consume a diet with higher ERDP scores may be at moderately increased risk of developing postmenopausal breast cancer, possibly through an influence on estrogen metabolism.

This is the first study to develop a dietary pattern based on estrogen metabolism that is specific to breast cancer risk, due to inclusion of the 2/16 ratio. Quantification of estrogen's downstream metabolic pathways that may be indicative of breast cancer risk was possible through use of a highly sensitive LC/MS-MS assay. Previously, Fung et al. used RRR to derive a dietary pattern correlated to serum estradiol and estrone sulfate. High scores for the pattern were characterized by high intakes of red meat, legumes, and pizza; and low intakes of whole grains and coffee. In the MPED food groups used in the ERDP, food items that

make up mixed dishes are decomposed into their individual food groups, (for example, pizza is decomposed into cheese, tomatoes, and refined grains). We observed moderate similarities between the ERDP and Fung et al.'s estrogen pattern with regard to cheese and tomatoes (in the form of pizza in Fung et al.'s pattern), coffee, and their respective directions of association with the derived patterns. Fung et al. observed an inverse association between whole grains and estrogen, and although whole grains were not a significant contributor to the ERDP, non-whole/refined grains had a significant positive association, suggesting the importance of choosing whole grains and limiting processed grains.

Other literature on dietary patterns and estrogen metabolism is scarce. However, the Alternate Healthy Eating Index and the Western pattern, comprised of processed foods and animal products, have been inversely and positively associated with serum estradiol, respectively.[23] An intervention study using the Mediterranean Diet, usually high in fruits and vegetables, legumes, oils, and other foods that result in a higher proportion of unsaturated fats compared to saturated fats, reported a roughly 40% decrease in total urinary estrogen levels ($p<0.02$) in postmenopausal women, showing some anti-estrogenic properties.[24] Although there is evidence linking alcohol [25] and soy products [26] with estrogen metabolism, they were not included in the ERDP because they failed to meet the inclusion criteria of a VIP >0.8 in the first RRR model. This indicated these groups did not explain a large enough variation in the EMs, possibly due to a small range of intakes for these groups in our subsample of women.

Evidence of a moderate but significant association between the ERDP and postmenopausal breast cancer was observed in our study population. A significant association was limited to ER+ subtypes, possibly due to an influence on estrogen metabolism. Fung et al.'s estrogen pattern was not associated with total postmenopausal breast or ER subtype-specific cancer risk in NHS,[12] which the authors concluded was a result of the low correlation between their pattern and the estrogens ($r=0.22$ and $r=0.24$ for estradiol and estrone sulfate, respectively), which may be insufficient to affect breast cancer risk. However, when the same pattern was applied in the Swedish Mammography Cohort (SMC) a 29% increase in risk of developing breast cancer (HR: 1.29; 95% CI: 1.08, 1.55) was observed when comparing women in the highest quartile with the lowest, and no heterogeneity was observed between the ER subtypes.[6] The authors cited a wider range of intakes, higher consumption of coffee, and lower levels of other breast cancer risk factors in SMC as reasons for results that differed from the NHS. Our results are consistent with those of the SMC. Explanations for different results between the previous studies and ours are difficult to discern because of our use of different EMs which resulted in different dietary patterns. The use of LC/MS-MS to accurately quantify the EMs, and inclusion of the 2/16 are strengths of our investigation. The 2/16 ratio represents the metabolism of parent estrogens down competing pathways with different physiologic properties, as exhibited by their metabolites, which may result in differences in breast cancer risk.[27] Three observational studies have investigated the relationship between the 2/16 ratio and postmenopausal breast cancer risk using LC/MS-MS. Two studies reported a 38% and 40% significant reduction in risk of postmenopausal breast cancer for higher categories of the 2/16 ratio,[16,28] with another study reporting a non-significant 37% reduction in risk ($p=0.10$).[29] Incorporation of the 2/16 ratio is a novel aspect

of the development of the ERDP and allows for the metabolism of estrogen to be considered, rather than only the parent estrogens.

Although the p-values for interaction were not statistically significant, qualitative evidence of effect modification by PHT, BMI, parity, and family history of breast cancer was observed in the association between the ERDP and postmenopausal breast cancer risk. Based on prior evidence, we expect women who are not using PHT or who are not obese to have lower lifetime exposure to estrogen.[30] In these women, a dietary influence through estrogen or other pathways may be easier to detect than in women with higher lifetime estrogen exposure. In the NHS, no effect modification by BMI was observed using their estrogen correlated dietary pattern, though other effect modifiers were not examined.[12] It is possible a woman's nulliparity is a result of low fertility due to low hormone levels.[31] However, nulliparous women typically experience more menstrual cycles, resulting in greater exposure to estrogen and higher breast cancer risk,[32] therefore these results need to be explored further. The association between the ERDP and postmenopausal breast cancer risk was observed in women who do not have a family history of breast cancer, but not in women with a family history, although the overall p-value for the interaction was not significant. Those with a family history of breast cancer have nearly twice the risk of developing postmenopausal breast cancer,[33] therefore, it is possible that the increase in risk associated with a family history of breast cancer may render a dietary association more difficult to detect. Evidence for dietary modification of risk among individuals with a family history of breast cancer or inherited genetic mutations is limited.[34–36]

There are multiple possible mechanisms by which the ERDP effects estrogen metabolism and breast cancer risk, such as through influences on microbiome diversity. The intestinal microbiome is strongly influenced by dietary behaviors, and the composition of the microbiome can have implications on many important physiological processes.[37] The fate of conjugated, or inactive, estrogens is dependent on the state of the intestinal microbiome, which influences whether or not the conjugated estrogens are excreted or transformed to their unconjugated forms and subsequently reabsorbed.[38] If reabsorbed, there is a greater estrogenic exposure throughout the body. Therefore, diet may influence development of a microbiome profile that is favorable to excretion of estrogens, lowering breast cancer risk, or one that is conducive to reabsorption of the estrogens which increases risk. In addition to absolute exposure to estrogen, the composition of EMs is also influenced by the microbiome. More specifically, there is evidence of microbial effects on interconversions of the parent estrogens and hydroxylation down the 16-pathway from in vitro and human studies.[39] The intestinal microbiome is strongly influenced by fiber intake, or lack thereof, through consumption of grains and vegetables, both of which are included in the ERDP.[37] The ERDP also is comprised of animal products, such as meats, cheese, and yogurt, which can impact microbiome diversity.[40,41] Considering the presence of a microbial influence on estrogen metabolism and its established relationship with diet, modification of the intestinal microbiome is a plausible mechanism by which the ERDP influences estrogen metabolism and breast cancer risk.

Considering other mechanisms, it is possible the ERDP was associated with breast cancer through effects on inflammation. Coffee, as well as processed meats, dairy, and refined

grains which are common in the Western diet, have all exhibited associations with inflammation, [42,43] and inflammation may play a role in mammary tumor development.[44] The Mediterranean Diet, characterized by foods with anti-inflammatory properties has been inversely associated with breast cancer, [45] and a dietary pattern based on inflammatory potential has shown evidence of an association with breast cancer [6] and breast cancer mortality.[47]

There are some limitations in our study that need to be considered when interpreting the results. As with most prospective nutritional investigations, there is the potential for bias due to the selection of subjects, loss to follow-up, and dietary measurement error. Although food frequency questionnaires may not generate accurate estimates for absolute intakes of nutrients, they have been shown to be effective in ranking individuals, as is the purpose in this study.[48] The development of data-driven dietary patterns, such as the ERDP, are dependent upon the population in which they were developed with respect to the foods included and their corresponding scoring weights. Therefore, the generalizability may be limited to the current population. Unexpected results from fish with low and high ω-3 fatty acids could have been due to preparation methods that were not ascertained. Low numbers of ER- cases may have limited our ability to detect an association in this subtype and a heterogeneity in effect by ER subtype, however, there were ample ER+ cases for analyses. A limitation of the PLCO study population is the lack of racial/ethnic diversity. However, non-Hispanic White women experience the highest incidence of breast cancer compared to other races/ethnicities in the US, so results are generalizable to this group at the highest risk.

There are strengths in the approach and design to note, as well. The use of a large, prospective cancer cohort allowed the associations of interest to be investigated with enough power to detect moderately small effects and with information on multiple known risk factors with which to adjust for potential confounding. The application of RRR to derive the ERDP provides the ability to incorporate a hypothesized pathogenic pathway in dietary pattern development.[11,49] As noted, the EMs included in the RRR models have been shown to be strongly related to breast cancer risk in a subset of this population, with a 107% increase in risk and a 38% reduction in risk observed when comparing high and low deciles for unconjugated E2 and the 2/16 ratio, respectively.[16] Furthermore, the EMs were measured using a more sensitive assay method, which is particularly important due to the low levels of EMs present in postmenopausal women, thus improving upon the previous RRR-derived estrogen dietary pattern.[12]

In conclusion, we identified a dietary pattern to be associated with an estrogen profile (high E2 and low 2/16 ratio) hypothesized to increase breast cancer risk. Women who had high ERDP scores tended to consume higher amounts of non-whole/refined grains, tomatoes, cheese, franks/luncheon meats; and lower amounts of nuts and seeds, cruciferous vegetables, other vegetables, fish/shellfish, yogurt, and coffee. A subsequent prospective investigation indicated that this estrogenic diet was associated with an increased risk of postmenopausal breast cancer risk, possibly through an influence on estrogen metabolism. Future studies should be conducted in populations from other regions with larger variation in intakes in food groups, or in study populations using open-ended dietary assessment tools to capture all foods or food groups that potentially influence estrogen metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

2/16	Ratio of 2- to 16-hydroxylated estrogen metabolites
BMI	Body mass index
CI	Confidence interval
DQX	Dietary questionnaire
E2	Estradiol
EM	Estrogen metabolite
ER	Estrogen receptor
ERDP	Estrogen-related dietary pattern
HR	Hazard ratio
LC/MS-MS	Liquid chromatography-tandem mass spectrometry

NHS	Nurses' Health Study
MPED	My Pyramid Equivalents Database
PHT	Postmenopausal hormone therapy
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
RRR	Reduced rank regression
SD	Standard deviation
SMC	Swedish Mammography Cohort
USDA	United States Department of Agriculture
VIP	Variable importance in projection

Novelty & Impact: Dietary investigations in breast cancer prevention have been inconclusive, therefore the authors sought to derive a dietary pattern based on a hypothesized mechanistic pathway. A diet based on an estrogen metabolism profile that is specific to breast cancer risk was characterized. Diets with intakes resulting in a high estrogen-related dietary pattern score were positively associated with breast cancer risk, with stronger effects in estrogen receptor positive cases and among strata of effect modifiers where estrogen exposure is lowest.

Table 1

Comparison of mean (±standard deviation) food or beverage intake across extreme quartiles of estrogen metabolites for the eleven foods and beverages included in the ERDP

		Unconjugated E2			2/16 Ratio		
	Model Weight[a]	Q1 (n=164)	Q4 (n=163)	p-value[b]	Q1 (n=163)	Q4 (n=163)	p-value[b]
Non-whole/refined grains (oz/day)	0.12	3.90 ± 1.81	4.45 ± 2.00	0.01	4.39 ± 2.06	4.10 ± 1.91	0.18
Tomatoes (cups/day)	0.09	0.40 ± 0.22	0.45 ± 0.27	0.06	0.43 ± 0.30	0.43 ± 0.24	0.79
Other vegetables (cups/day)	-0.13	0.96 ± 0.52	0.95 ± 0.45	0.89	1.02 ± 0.58	1.07 ± 0.60	0.42
Cruciferous vegetables (cups/day)	0.08	0.28 ± 0.21	0.26 ± 0.20	0.6	0.30 ± 0.26	0.32 ± 0.23	0.46
Cheese (cups/day)	0.16	0.29 ± 0.23	0.43 ± 0.38	<0.01	0.38 ± 0.37	0.33 ± 0.26	0.2
Yogurt (cups/day)	-0.12	0.12 ± 0.19	0.08 ± 0.15	0.03	0.09 ± 0.17	0.12 ± 0.21	0.15
Fish/shellfish high in ω-3 fatty cids (oz/day)	0.2	0.16 ± 0.17	0.15 ± 0.15	0.55	0.15 ± 0.17	0.16 ± 0.19	0.53
Fish/shellfish low in ω-3 fatty cids (oz/day)	-0.27	0.53 ± 0.47	0.49 ± 0.38	0.46	0.46 ± 0.36	0.52 ± 0.49	0.21
Franks and luncheon meats (oz/day)	0.08	0.21 ± 0.23	0.34 ± 0.56	0.01	0.28 ± 0.31	0.22 ± 0.28	0.07
Nuts and seeds (oz/day)	-0.11	0.45 ± 0.70	0.38 ± 0.42	0.32	0.44 ± 0.79	0.44 ± 0.64	0.99
Coffee (cups/day)	-0.1	3.09 ± 3.59	2.30 ± 3.27	0.04	2.64 ± 3.34	3.18 ± 3.73	0.17

ERDP: estrogen related dietary pattern

[a] Model weight from final RRR model that is used for ERDP scoring.

[b] t-test for the comparison of means in the first and fourth quartiles.

Table 2

PLCO population characteristics across the ERDP quartiles

		ERDP Quartile (score range)			
		1st (-4.515, 0.350)	**2nd (-0.351, 0.021)**	**3rd (-0.022, 0.328)**	**4th (0.329, 6.578)**
n		6,872	6,872	6,872	6,872
Breast cancer cases	Total	366	392	403	431
	Invasive	280	309	331	348
	ER+	246	275	274	302
	ER-	45	41	55	48
ERDP score (mean ± SD)		-0.77 ± 0.43	-0.18 ± 0.09	0.14 ± 0.10	0.77 ± 0.48
Age (mean ± SD)		62.6 ± 5.3	62.8 ± 5.4	62.5 ±5.3	61.8 ± 5.2
BMI (kg/m^2; mean ± SD)		26.6 ± 5.1	26.6 ± 5.1	27.1 ± 5.3	28.1 ± 5.9
BMI at age 20 (kg/m^2; mean ± SD)		21.4 ± 2.9	21.1 ± 2.7	21.2 ± 2.7	21.4 ± 3.0
Total energy intake (kcal/day; mean ± SD)		1,691 ± 578	1,542 ± 528	1,659 ± 535	2,078 ± 621
PHT use (%)					
	Current	51.7	51.9	51.6	51.6
	Former	15.8	16.4	16	15.8
	Never	32	31.3	32	32.1
Race (%)					
	White, Non-Hispanic	88.4	90.6	91.9	93.1
	Black, Non-Hispanic	4.8	4.5	4.1	3.9
	Hispanic	1.1	1.2	1.4	1.4
	Asian	5.1	3.1	2.1	1.1
Alcohol (%)					
	Abstainer	24.4	25.7	28.7	29.9
	0-7 drinks/week	62.4	60.8	58.4	55.5
	>7 drinks/week	13.2	13.5	12.9	14.6
Smoking (%)					
	Current	9.6	8.8	7.8	9.3
	Former	38.7	33.7	31.8	32.4

		ERDP Quartile (score range)			
		1st (-4.515, 0.350)	**2nd (-0.351, 0.021)**	**3rd (-0.022, 0.328)**	**4th (0.329, 6.578)**
	Never	51.7	57.5	60.4	58.3
Education (%)					
	< High school	5.4	5.8	5.9	5.6
	High school grad and some college	62.2	65.2	65.2	64
	College grad	15.9	15.3	15.6	16.1
	Postgraduate	16.6	13.8	13.4	14.3
Live births (%)					
	None	9.9	8.8	8.5	8.6
	1	7.4	6.6	7	7.2
	2	24.6	23.8	23.1	22.7
	3	25.2	25.4	25.3	25.5
	≥ 4	32.9	35.4	36.1	36
Age at menopause (%)					
	< 40	14.4	14	13.3	13.3
	40-44	14.3	13.6	14.5	13.4
	45-59	23.9	23.9	23.2	23.2
	50-54	36.2	37.3	37.9	38.2
	≥55	11.2	11.3	11.2	12
Family history of breast cancer (%)					
	No	85	85.7	84.6	84.3
	Yes, immediate female	13.9	13.4	14.1	14.5
	Male only	0.2	0.1	0.2	0.1
Bilateral oophorectomy (%)					
	No	90.3	88.9	88.5	88.3
	Yes	9.8	11.1	11.5	11.7
Hours of vigorous PA per week (%)					
	None	12.2	14.5	15.6	19.4
	< 1	16.3	18.9	19.4	19.7
	1	11.3	12.4	11.7	12.3

	ERDP Quartile (score range)			
	1st (-4.515, 0.350)	**2nd (-0.351, 0.021)**	**3rd (-0.022, 0.328)**	**4th (0.329, 6.578)**
2	17.7	16.5	17	16.1
3	17.8	16.7	17	14.9
≥4	24.9	21	19.3	17.6
Non-whole/refined grains (oz/day; mean ± SD)	3.51 ± 1.58	3.50 ± 1.52	4.10 ± 1.60	5.66 ± 2.19
Tomatoes (cups/day; mean ± SD)	0.38 ± 0.23	0.36 ± 0.22	0.41 ± 0.24	0.56 ± 0.42
Other vegetables (cups/day; mean ± SD)	1.14 ± 0.64	0.93 ± 0.51	0.90 ± 0.48	0.98 ± 0.52
Cruciferous vegetables (cups/day; mean ± SD)	0.30 ± 0.28	0.27 ± 0.24	0.27 ± 0.24	0.30 ± 0.28
Cheese (cups/day; mean ± SD)	0.23 ± 0.18	0.24 ± 0.18	0.32 ± 0.21	0.60 ± 0.40
Yogurt (cups/day; mean ± SD)	0.25 ± 0.30	0.10 ± 0.15	0.07 ± 0.12	0.06 ± 0.12
Fish/shellfish high in ω-3 fatty acids (oz/day; mean ± SD)	0.19 ± 0.21	0.14 ± 0.15	0.13 ± 0.15	0.17 ± 0.22
Fish/shellfish low in ω-3 fatty acids (oz/day; mean ± SD)	0.65 ± 0.63	0.45 ± 0.37	0.43 ± 0.35	0.49 ± 0.42
Franks and luncheon meats (oz/day; mean ± SD)	0.14 ± 0.17	0.16 ± 0.17	0.22 ± 0.22	0.42 ± 0.45
Nuts and seeds (oz/day; mean ± SD)	0.63 ± 0.97	0.35 ± 0.48	0.33 ± 0.42	0.38 ± 0.45
Coffee (cups/day; mean ± SD)	3.83 ± 4.22	2.37 ± 2.50	1.86 ± 2.18	1.86 ± 2.29

ERDP: estrogen related dietary pattern; ER: estrogen receptor; BMI: body mass index; PHT: postmenopausal hormone therapy; PA: physical activity; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SD: standard deviation

Table 3

Hazard ratios (95% CI) for the relationship between the ERDP score and postmenopausal breast cancer in PLCO

	ERDP quartiles				Estimate for continuous ERDP score[a], p-trend
	1st	2nd	3rd	4th	
Total breast cancer					
No. of cases	366	392	403	431	
Age-adjusted	1.00 (ref)	1.07 (0.93, 1.24)	1.10 (0.95, 1.26)	1.18 (1.03, 1.36)	1.12 (1.03, 1.20) p=0.005
Age- and-TEI adjusted	1.00 (ref)	1.09 (0.94, 1.25)	1.10 (0.95, 1.27)	1.15 (1.00, 1.33)	1.10 (1.01, 1.18) p=0.02
Multivariable-adjusted[b]	1.00 (ref)	1.08 (0.94, 1.25)	1.10 (0.95, 1.27)	1.14 (0.98, 1.32)	1.09 (1.01, 1.18) p=0.04
Invasive					
No. of cases	280	309	331	348	
Age-adjusted	1.00 (ref)	1.11 (0.94, 1.30)	1.18 (1.00, 1.38)	1.25 (1.07, 1.47)	1.16 (1.07, 1.26) p=0.0006
Age- and-TEI adjusted	1.00 (ref)	1.12 (0.95, 1.32)	1.18 (1.01, 1.38)	1.21 (1.03, 1.43)	1.14 (1.04, 1.24) p=0.003
Multivariable-adjusted[b]	1.00 (ref)	1.12 (0.95, 1.31)	1.18 (1.01, 1.39)	1.20 (1.02, 1.42)	1.13 (1.04, 1.24) p=0.005
ER+					
No. of cases	246	275	274	302	
Age-adjusted	1.00 (ref)	1.12 (0.94, 1.33)	1.11 (0.93, 1.32)	1.23 (1.04, 1.46)	1.15 (1.05, 1.26) p=0.003
Age- and-TEI adjusted	1.00 (ref)	1.13 (0.95, 1.35)	1.11 (0.94, 1.32)	1.20 (1.01, 1.42)	1.13 (1.03, 1.24) p=0.01
Multivariable-adjusted[b]	1.00 (ref)	1.13 (0.95, 1.34)	1.11 (0.94, 1.32)	1.19 (0.99, 1.41)	1.13 (1.02, 1.24) p=0.02
ER-					
No. of cases	45	41	55	48	
Age-adjusted	1.00 (ref)	0.92 (0.60, 1.40)	1.21 (0.82, 1.80)	1.06 (0.71, 1.59)	1.09 (0.87, 1.35) p=0.46
Age- and-TEI adjusted	1.00 (ref)	0.93 (0.61, 1.43)	1.22 (0.82, 1.81)	1.01 (0.66, 1.53)	1.06 (0.85, 1.32) p=0.63
Multivariable-adjusted[b]	1.00 (ref)	0.94 (0.61, 1.44)	1.24 (0.83, 1.84)	1.04 (0.68, 1.59)	1.07 (0.85, 1.35) p=0.54
Person-years accumulated	74,615	74,375	74,932	74,468	

ERDP: estrogen related dietary pattern; TEI: total energy intake; ER: estrogen receptor; BMI: body mass index; PHT: postmenopausal hormone therapy; PA: physical activity; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

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

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

Table 4

Hazard ratios (95% CI) for the relationship between the ERDP score and postmenopausal breast cancer within strata of estrogen-related risk factors and by family history of breast cancer in PLCO[a]

	ERDP quartiles				p interaction[b]
	1st	2nd	3rd	4th	
PHT use at baseline					0.64
No	1.00 (ref)	1.20 (0.96, 1.50)	1.27 (1.02, 1.59)	1.24 (0.99, 1.56)	
Yes	1.00 (ref)	1.02 (0.85, 1.23)	1.01 (0.84, 1.21)	1.07 (0.88, 1.29)	
BMI (kg/m^2)					0.59
18.5-29.9	1.00 (ref)	1.09 (0.92, 1.28)	1.14 (0.97, 1.34)	1.20 (1.02, 1.43)	
≥30	1.00 (ref)	1.12 (0.83, 1.51)	1.01 (0.75, 1.35)	0.99 (0.75, 1.32)	
Alcohol consumption					0.90
<1 drink/week	1.00 (ref)	1.11 (0.92, 1.34)	1.15 (0.96, 1.38)	1.15 (0.95, 1.39)	
≥1 drinks/week	1.00 (ref)	1.05 (0.84, 1.32)	1.03 (0.82, 1.30)	1.14 (0.90, 1.44)	
Parity					0.58
Nulliparous	1.00 (ref)	1.24 (0.77, 2.00)	1.44 (0.90, 2.28)	1.45 (0.91, 2.32)	
Parous	1.00 (ref)	1.06 (0.91, 1.24)	1.07 (0.92, 1.24)	1.10 (0.95, 1.28)	
Vigorous PA					0.61
<2 hours/week	1.00 (ref)	1.18 (0.95, 1.47)	1.11 (0.89, 1.38)	1.12 (0.90, 1.40)	
≥2 hours/week	1.00 (ref)	1.01 (0.83, 1.22)	1.10 (0.91, 1.33)	1.17 (0.96, 1.42)	
Family history of breast cancer					
No	1.00 (ref)	1.11 (0.95, 1.30)	1.11 (0.95, 1.30)	1.17 (0.99, 1.37)	0.94
Yes	1.00 (ref)	1.00 (0.71, 1.42)	1.05 (0.75, 1.47)	1.03 (0.73, 1.45)	

ERDP: estrogen related dietary pattern; TEI: total energy intake; ER: estrogen receptor; BMI: body mass index; PHT: postmenopausal hormone therapy; PA: physical activity; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

[a]Includes adjustment for age, TEI, BMI, BMI at age 20, PHT, alcohol use, education, bilateral oophorectomy, parity, age at menopause, PA, race/ethnicity, recruitment center, and family history of breast cancer

[b]P-value for the product term of ERDP quartiles with the potential effect modifier.