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Dietary inflammatory potential, oxidative balance score, and risk of breast cancer: findings from the Sister Study

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Abstract

Diet, inflammation, and oxidative stress may be important in breast carcinogenesis, but evidence on the role of the inflammatory and pro-oxidative potential of dietary patterns is limited.

Energy adjusted-Dietary Inflammatory Index (E-DII ™) and dietary oxidative balance score (D-OBS) were calculated for 43,563 Sister Study cohort participants who completed a Block 1998 food frequency questionnaire at enrollment in 2003–2009 and satisfied eligibility criteria. D-OBS was validated using measured F_2-isoprostanes and metabolites. High E-DII score and low D-OBS

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Ethics Statement: The Sister Study is overseen by the NIH Institutional Review Board. All participants provided written informed consent.

represent a more pro-inflammatory and pro-oxidant diet, respectively, and associations of quartiles of each index with breast cancer (BC) risk were estimated using multivariable Cox proportional hazards regression.

There were 2,619 BCs diagnosed at least 1 year after enrollment (mean follow-up 8.4 years). There was no overall association between E-DII and BC risk, whereas there was a suggestive inverse association for the highest versus lowest quartile of D-OBS (HR 0.92 [95% CI, 0.81–1.03]). The highest quartile of E-DII was associated with risk of triple-negative BC (HR 1.53 [95% CI, 0.99–2.35]). When the two indices were combined, a pro-inflammatory/pro-oxidant diet (highest tertile of E-DII and lowest tertile of D-OBS) was associated with increased risk for all BC (HR 1.13 [95% CI, 1.00–1.27]) and for triple-negative BC (1.72 [95% CI, 1.10–2.70]), compared with an anti-inflammatory/anti-oxidant diet (lowest tertile of E-DII and highest tertile of D-OBS).

Diets with increased inflammatory potential and reduced oxidative balance were positively associated with overall and triple-negative BC.

Keywords

dietary inflammatory potential; oxidative balance score; breast cancer; estrogen receptor; triple-negative

INTRODUCTION

Chronic inflammation may promote cancer development and progression. [1] Epidemiologic evidence shows that inflammatory markers such as C-reactive protein (CRP) are associated with increased risk of breast cancer. [2] Dietary composition has been associated with inflammatory markers, [3] and healthy dietary patterns are associated with lower levels of inflammation. [45] The dietary inflammatory index (DII®), a dietary index developed based on peer-reviewed research focusing on diet and inflammation, [6] provides a novel approach for evaluating the inflammatory potential of diet, and has been shown to predict several inflammatory biomarkers. [7] The DII has been consistently associated with increased risk of colorectal cancer [89], but there have been conflicting results for breast cancer risk, particularly from prospective cohort studies. [9101112]

Oxidative stress is a state of imbalance between antioxidants and oxidative damage. Under oxidative conditions, prooxidants are dominant over antioxidants, potentially leading to damage to lipids, proteins, or directly to DNA. [13] These oxidative stress mechanisms may contribute to carcinogenesis. [14] The oxidative balance score (OBS) was developed to quantify an individual's oxidative stress burden using dietary and lifestyle anti- and pro-oxidant factors. [1516] Although numerous studies have evaluated the association between OBS and various health outcomes, [17] few studies have investigated the association between dietary OBS (D-OBS) and breast cancer risk. [1819]

Because both inflammation and oxidative stress play an important role in increasing the risk of cancer, it is plausible that the DII and D-OBS could act together to influence breast cancer risk. However, few studies have examined this joint association. [20] Furthermore, potential differential associations by breast cancer subtype have been rarely addressed in

studies of the DII and/or D-OBS even though breast cancers may have different etiological and clinical characteristics according to hormone receptor status. [21, 22]

Therefore, we examined the association of the energy adjusted (E-DII™), D-OBS, individually and in combination, in relation to risk of breast cancer, using data from the nationwide prospective Sister Study cohort.

MATERIALS AND METHODS

Study population

This study was based in the Sister Study, a nationwide prospective cohort study that evaluates environmental and genetic risk factors for breast cancer. [23] A total of 50,884 women who are sisters or half-sisters of women diagnosed with breast cancer were enrolled across the US and Puerto Rico between 2003 and 2009. Eligible participants were 35–74 years old at enrollment and did not have breast cancer themselves. Details of the study design, data collection, and outcome measurements are described elsewhere. [23, 24] Study participants had anthropometric measurements and provided biological samples in a home exam and completed telephone interviews, and written questionnaires on demographic, medical, lifestyle, and reproductive history at enrollment. Participants completed annual health updates and comprehensive follow-up questionnaires every 2 to 3 years to update information on risk factors and changes in health status. Response rates have been around 90% throughout follow-up. [23]

Dietary assessment

Dietary consumption was measured at baseline using a modified 1998 Block 110-item food frequency questionnaire (FFQ). [25] This FFQ has been previously validated in women [26]. Participants were asked to report their average dietary intake in the past 12 months of each listed food and beverage item, including the frequency (9 possible frequencies, ranging from “never” to “every day”) and the quantity (portion size) specified (3 or 4 quantity choices per food item or group of similar food items). Nutrient consumption was estimated based on FFQ responses using the United States Department of Agriculture Food and Nutrient Database for Dietary Studies for US women. [27]

Assessment of Dietary Inflammatory Index (DII®) and Dietary Oxidative Balance Score (D-OBS)

The development of the DII has been described elsewhere.[6] The DII is a literature-derived, population-based score developed to characterize the inflammatory potential of diet, considering the association of food parameters (i.e., micronutrients, macronutrients, some bioactive components or individual foods) with six inflammatory biomarkers (tumor necrosis factor-α, CRP, interleukin [IL]-10, IL-6, IL-4 and IL-1β). Based on comprehensive literature review of 1943 peer-reviewed articles published through 2010, inflammatory effect scores for 45 food parameters (components of the DII) were derived. Then, reported dietary consumption data derived from a modified 1998 Block 110-item FFQ were standardized to a representative range of dietary intakes based on 11 datasets from diverse populations in different countries across the world. The DII was construct-validated using inflammatory

biomarkers such as high-sensitivity CRP and IL-6. [2829] E-DII scores were calculated after converting consumption of the food parameters to an amount per 1000 kcal of energy intake. A total of 31 food parameters were used to calculate E-DII in this study: carbohydrate, cholesterol, energy, total fat, iron, protein, saturated fat, trans fat, alcohol, β-carotene, caffeine, fiber, folic acid, magnesium, MUFA, niacin, n-3 fatty acids, n-6 fatty acids, PUFA, riboflavin, selenium, thiamin, vitamins A, B6, B12, C, D, and E, zinc, isoflavones, and tea.

We calculated the D-OBS by integrating 17 *a priori* defined pro- and antioxidant factors (Supplementary Table 1) [1617] The pro-oxidants consisted of saturated fats, the ratio of polyunsaturated n-6 fatty acid to n-3 fatty acid, total (food and supplement) iron, and alcohol consumption. The antioxidants included total vitamin C, total vitamin E, total vitamin D, total selenium, total zinc, total calcium, total β-carotene, total lycopene, α-carotene, lutein & zeaxanthin, cryptoxanthin, retinol, and gamma-tocopherol. Smoking, use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, all of which were included in the original OBS were adjusted for in the statistical models. We categorized continuous dietary variables into quartiles after converting consumption of each factor to an amount per 1000 kcal of energy intake. Pro-oxidants were assigned points from 3 to 0 for the first through fourth quartiles, respectively, whereas antioxidants were scored in reverse. For alcohol consumption, nondrinkers received 3 points, current drinkers with < 1 drink/day received 2 points, current drinkers with 1 drink/day received 1 point, and current drinkers with >1 drink/day received 0 points. The overall D-OBS was calculated by summing the points assigned for each component. Higher D-OBS indicates greater antioxidant exposure.

To explore the risk of breast cancer in women with proinflammatory and prooxidative diets compared with those with anti-inflammatory and anti-oxidative diets, we created a composite variable using the E-DII and D-OBS. Women in the upper tertile of DII and the lower tertile of D-OBS were classified as having a proinflammatory and prooxidative diet, whereas women in the lower tertile of DII and the upper tertile of D-OBS were classified as having an anti-inflammatory and anti-oxidative diet. Everyone else was classified into an intermediate category.

Validation of D-OBS using oxidative stress biomarkers for a sub-population of participants

Because no construct validation data are available for the D-OBS as implemented in the present study, we examined whether D-OBS is associated with the oxidative stress biomarker F_2-isoprostane and the F_2-isoprostane metabolite using measurements obtained for other Sister Study research. [3031] Participants provided first morning urine samples at enrollment. Samples from 910 premenopausal women included as controls in a nested case-control study were retrieved in 2012 [31] and samples from 524 randomly sampled postmenopausal women were randomly retrieved in 2018. [30] Urinary 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) and its metabolite (8-iso-$PGF_{2\alpha}$-M) concentrations were measured at the Eicosanoid Core Laboratory at Vanderbilt University Medical Center by gas chromatography/ negative ion chemical ionization mass spectrometry (GC/MS) for samples from premenopausal participants and liquid chromatography/ negative ion chemical ionization mass spectrometry (LC/MS) for samples from postmenopausal participants. Detailed protocols for these methods have been published. [3233] All values of 8-iso-$PGF_{2\alpha}$

and 8-iso-$PGF_{2\alpha}$-M were adjusted for urine creatinine concentrations to account for urine diluteness.

Assessment of breast cancer

Breast cancer diagnoses were self-reported and confirmed by medical records. Medical records have been obtained for more than 80% of cases to date. Agreement between self-reported breast cancer and medical records was high (positive predictive value over 99% for overall) and thus self-report was used when medical records were not available. [2434] Follow-up was through September 15, 2017 (data release 7.1). Cancer subtypes were defined according to estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) status. When breast cancers were tested negative for all these markers, they were classified as triple-negative.

Statistical Analysis

We excluded women who did not provide an FFQ (n=1,143), reported implausibly extreme energy intakes (<500 and >3500 kcals/d) (n=1,015), skipped more than half of FFQ items (n=230), were pregnant or breastfeeding (n=58) at baseline, had extreme body mass index (BMI) values (<15 or >50 kg/m^2) (n=303), had a history of any cancer except non-melanoma skin cancer at baseline (n=2,771), or reported a breast cancer with unknown timing or uncertain diagnosis (n=6). To reduce bias from reverse causality related to undetected tumors present at baseline (which could have influenced diet or other factors), we began follow-up 12 months after enrollment, thereby excluding 361 incident cases and 252 other women with short follow-up. A total of 43,563 women were included in the analysis after further excluding women with missing covariate data (3.5 % of individuals). Person-time was calculated from the age one year after enrollment until the age of breast cancer diagnosis, age at death, loss to follow-up, whichever occurred first. If a participant was diagnosed with one type of breast cancer, they were censored for all other types of breast cancer at the time of diagnosis.

In the validation substudy, separate linear regression models were used to assess the association between D-OBS and urinary oxidative stress markers in pre-and postmenopausal women (n=884 and 512, respectively) with log-transformed urinary 8-iso-$PGF_{2\alpha}$ and 8-iso-$PGF_{2\alpha}$-M as the dependent variable after adjusting for age at urine sample, race/ethnicity (non-Hispanic White, non-Hispanic Black, or other than White or Black), education (high school or less, some college, or 4-year degree or higher), objectively-measured BMI (continuous), smoking status (never smoker, <10 pack-years, <20 and ≥10 pack-years ≥20 pack-years), self-reported leisure-time physical activity (metabolic equivalent hours/week, quintile), hormone therapy (none, estrogen only, both estrogen and progesterone), use of aspirin (never, tertiles of lifetime cumulative doses, or missing), use of non-aspirin NSAIDs (never, tertiles of lifetime cumulative doses, or missing), and creatinine concentration after excluding those with implausibly extreme energy intakes (<500 and >3500 kcals/d).

In the full study population, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between DII score, D-OBS and breast cancer risk using Cox proportional hazards regression with age as the primary time scale. Quartiles and continuous

measures of DII and D-OBS (using a 1 standard deviation [SD] increment) were used to characterize diet measures. Proportional hazards assumptions were evaluated by Schoenfeld residuals with the logarithm of the cumulative hazards function based on Kaplan-Meier estimates for DII score and D-OBS. We did not detect any significant departures from proportionality in hazards over time.

Potential confounders or effect modifiers were identified *a priori* based on literature review and presumed causal relationships among the covariates.[35] The following covariates at baseline were included in multivariable-adjusted models: race/ethnicity, education, objectively-measured BMI (continuous), menopausal status (binary), an interaction term between BMI and menopausal status, smoking status, self-reported physical activity, number of first-degree relatives diagnosed with breast cancer before age 50 years (0, ≥1), recent mammogram screening (<1, 1–2, or > 2 years or never had a mammogram), ever use of hormonal birth control, hormone therapy (none, estrogen only, both estrogen and progesterone), use of aspirin (never, tertiles of lifetime cumulative dose, or missing), and use of non-aspirin NSAIDs (never, tertiles of lifetime cumulative dose, or missing).

Tests for linear trend across quartiles of the DII and D-OBS were performed by modeling the median value of each quartile. Potential effect modification was evaluated with likelihood ratio tests for menopausal status, race/ethnicity, degree of family history of breast cancer, BMI, physical activity, and alcohol consumption. Menopausal status was analyzed as a time-varying exposure that contributed to follow-up time at risk for either premenopausal or postmenopausal breast cancer and was considered for both incident cases and non-cases. A case-case analysis was applied to explore etiological heterogeneity in the association between DII, D-OBS, and breast cancer by ER status. [36]

We conducted sensitivity analyses that restricted the outcome to women with invasive breast cancer or that included all reproductive risk factors including age at menarche, age at first live birth, breastfeeding history, use of birth control pill, and parity as covariates. We also performed a sensitivity analysis with an additional adjustment for Healthy Eating Index (HEI)-2015 to explore associations after adjusting for overall diet quality. Statistical significance was evaluated with two-sided tests, with the level of significance set at 0.05. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics are presented in Table 1 stratified by E-DII and D-OBS, respectively. Women with higher E-DII scores (more pro-inflammatory diet) were younger, less physically active, and had a higher BMI, shorter lifetime duration of breastfeeding, and younger age at menopause. They were less likely to be non-Hispanic White, and were more likely to have less education, to have smoked, and to have used hormone therapy in the past (Table 1). They also were less likely to have recent mammogram screening and were more likely to have a first-degree female member diagnosed with breast cancer before age 50. There was a strong inverse correlation between DII and D-OBS (Pearson correlation coefficients= −0.80). Women with higher E-DII scores tended to consume more red and processed meats, refined grains, added sugars, and less fruits, vegetables, whole grains, nuts

and legumes, and seafood high in n-3 fatty acids. An opposite trend was seen in women with higher D-OBS. E-DII scores were inversely correlated with HEI-2015 scores (r = –0.34) and D-OBS was positively correlated with HEI-2015 scores (r=0.53) (Supplementary Table 2).

The geometric mean concentrations of 8-iso-$PGF_{2\alpha}$ and 8-iso-$PGF_{2\alpha}$-M and their associations with quartiles of D-OBS in a sample of premenopausal participants (n=884) and a representative sample of postmenopausal participants (n=519) are shown in Table 2. Both 8-iso-$PGF_{2\alpha}$ and 8-iso-$PGF_{2\alpha}$-M were inversely associated with increasing quartiles of D-OBS in premenopausal and postmenopausal women (P for trend <0.001 and 0.001, respectively).

A total of 2,619 incident breast cancer cases (invasive and ductal carcinoma *in-situ*) were identified during follow-up from 1 year after enrollment (mean, 8.4 years). Associations between E-DII and D-OBS quartiles and breast cancer are shown in Table 3. There was no overall association between E-DII score and breast cancer risk in either categorical or continuous analysis. There was a suggestive positive association between E-DII and ER– breast cancer risk ($HR_{\text{highest vs. lowest quartile}}$: 1.30, 95% CI 0.94–1.79; $HR_{\text{1SD increase}}$: 1.09, 95% CI: 0.97–1.22) but not ER+ breast cancer risk. The positive association was stronger for triple-negative breast cancer (TNBC) ($HR_{\text{highest vs. lowest quartile}}$ 1.53; 95% CI 0.99–2.35; $HR_{\text{1SD increase}}$: 1.18; 95% CI 1.03–1.36). The HR comparing the highest to the lowest quartile of D-OBS was 0.92 (95% CI 0.81–1.03; $HR_{\text{1SD increase}}$: 0.97; 95% CI 0.93–1.01). This inverse association was more apparent for TNBC ($HR_{\text{highest vs. lowest quartile}}$ 0.74; 95% CI 0.48–1.15; $HR_{\text{1SD increase}}$: 0.88; 95% CI 0.76–1.02), though neither was statistically significant. Associations with E-DII varied somewhat by menopause status and there was an inverse association between E-DII and ER+ breast cancer in premenopausal women (Supplementary Table 3). The D-OBS was inversely associated with postmenopausal breast cancer risk but positively associated with premenopausal risk (Supplementary Table 3).

Associations between E-DII and D-OBS combined and risk of breast cancer are shown in Table 4. Women with both pro-inflammatory and pro-oxidant diet (the upper tertile of DII and the lower tertile of D-OBS) had higher risk of overall breast cancer compared with those with anti-inflammatory and anti-oxidative diet (the lower tertile of DII and the upper tertile of D-OBS) (HR 1.13; 95% CI 1.00–1.27). The association with the combined diet category was limited to ER– breast cancer (HR 1.39 [95% CI 1.00–1.93] for ER– breast cancer vs. HR 1.05 [95% CI 0.91–1.21] for ER+ breast cancer; P-heterogeneity =0.03), and stronger for TNBC (HR 1.72; 95% CI 1.10–2.70). Pro-inflammatory and pro-oxidant diet showed stronger positive associations with postmenopausal breast cancer, whereas it was inversely associated with premenopausal breast cancer (Supplementary Table 4).

Results based on the stratified analyses for the association between pro-inflammatory and pro-oxidant diet and breast cancer risk are shown for menopausal status, race/ethnicity, obesity, degree of family history, physical activity, and alcohol consumption (Table 5). A positive association was observed for postmenopausal breast cancer (HR 1.20; 95% CI 1.05–1.37); whereas an inverse association was observed for premenopausal breast cancer (HR 0.65; 95% CI 0.49–0.87 P for interaction=0.001). Overweight and obese women with pro-inflammatory and pro-oxidant diets showed higher risk of breast cancer compared with those

with anti-inflammatory and anti-oxidative diet (HR 1.28; 95% CI 1.10–1.48; P for interaction=0.05). Although interactions were not statistically significant, the associations between pro-inflammatory and pro-oxidant diets and breast cancer appeared stronger among non-Hispanic Black women (HR 1.41; 95% CI 0.87–2.30) and women who identified as a race/ethnicity other than White or Black (HR 1.73; 95% CI 1.01–2.97), women with low to moderate physical activity (HR 1.20; 95% CI 1.05–1.38), and women without current alcohol consumption (HR 1.42; 95% CI 1.07–1.88).

Sensitivity analyses with an additional adjustment for the HEI-2015 also did not materially change the overall results (Supplementary Table 5). Sensitivity analysis with additional adjustment for all reproductive risk factors did not materially alter the overall results (data not shown). The results were not materially changed in analyses limited to invasive breast cancer (data not shown).

DISCUSSION

In this nationwide prospective cohort study, we found that the E-DII was not associated with overall breast cancer, although there was a suggestive increased risk of ER– breast cancer and TNBC. In contrast, D-OBS was associated with a suggestive decreased risk of overall breast cancer and this association was stronger for TNBC. In addition, a combined pro-inflammatory and pro-oxidant diet classified as higher E-DII score and lower D-OBS was associated with increased risk of breast cancer, especially ER– breast cancer and TNBC. The positive association between pro-inflammatory and pro-oxidant diet and breast cancer risk was clearer for postmenopausal breast cancer.

Several recent meta-analyses on the association between the DII and breast cancer reported that the DII may not be associated with overall breast cancer risk, especially based on findings from prospective cohort studies. [101112] Only a few studies have evaluated the association between the DII and breast cancer risk by hormone receptor status. The Women's Health Initiative showed a slightly increased risk in ER– cancer (HR 1.13; 95% CI 0.91, 1.41) compared with ER+ cancer (HR 0.97; 95% CI 0.89, 1.06) in women with high consumption of proinflammatory diet. [37] Another study in the same population showed that having a proinflammatory diet at baseline was associated with increased risk of TNBC (HR 1.40; 95% CI 0.90, 2.19) an association that persisted when considering proinflammatory diet during follow-up (HR 1.39; 95% CI 0.95, 2.04). [38] In contrast, findings from case-control studies from South Korea [39] and China [40] showed that the DII was positively associated with both ER+/PR+ and ER–/PR– cancers. It is unclear whether the difference results by hormonal status are due to different study designs or population differences. However, a variety of measures of diet quality have been associated with ER– breast cancer in prospective cohort studies comprising women from Europe and the US. [41] In addition, higher DII score has been related to increased levels of inflammatory biomarkers, which are more strongly associated with ER– than ER+ breast cancer. [742]

Few studies have investigated D-OBS in association with breast cancer risk. In a case-control study in Mexico and the U.S. comprising 2,111 Hispanic and 1,481 non-Hispanic White breast cancer cases, there was an inverse association between higher D-OBS and

breast cancer risk (odds ratio 0.74, 95% CI 0.64–0.84). [18] In a prospective cohort study among 3,209 participants in the Netherlands, higher dietary antioxidant capacity measured by the ferric reducing antioxidant potential instead of D-OBS was also associated with decreased risk of breast cancer (HR 0.68; 95% CI 0.49–0.96). [43] However, associations by hormonal status were not evaluated in either study.

Estimates for breast cancer risk based on combining the E-DII and D-OBS (i.e., comparison of proinflammatory and prooxidative diet with anti-inflammatory and anti-oxidative diet) were stronger than those for the associations observed for the individual indices, especially for ER–breast cancer and TNBC, although there was no statistical interaction between the two indices. It should also be noted that when women had either higher E-DII score or lower D-OBS, alone, they still had a higher estimated risk of breast cancer. In contrast, in a previous case-control study in Spain, the association using a profile score combining the E-DII and antioxidant capacity in relation to breast cancer risk was not strengthened compared to that obtained when using E-DII alone. [20]

In our study, the association of the DII and the combination of DII and D-OBS with risk of breast cancer was more pronounced for hormone receptor-negative cancer, especially for TNBC. Compared to ER+ cancers, ER– cancers are more weakly associated with reproductive risk factors related to estrogen levels. Thus, it has been suggested that hormone-independent mitogenic pathways through the epidermal growth factor family of receptors and related nuclear factor kB activation may play an important role in ER– carcinogenesis. [44] Biological evidence also suggests that inflammation and oxidative stress may be involved in ER– cancer development. [4546] We also reported that recommendation-based dietary indices including Dietary Approaches to Stop Hypertension diet, Alternative Mediterranean Diet, and Alternative Healthy Eating Index–2010 as well as mechanism-based dietary index such as diet-dependent acid load were exclusively associated with ER– breast cancer and TNBC. [4748] Because these dietary indices share common dietary components such as non-starchy vegetables and carotenoids that are known to be exclusively associated with ER– cancer, [4950] these components and related phytochemicals may contribute to differential association by ER status in the present study.

In stratified analyses in our study, pro-inflammatory and pro-oxidant diet was positively associated with postmenopausal breast cancer, whereas it was inversely associated with premenopausal breast cancer (Supplementary Table 4). Similar associations were observed when E-DII and D-OBS were analyzed separately (Supplementary Table 3). A case-control study using the profile score combining the E-DII and antioxidants capacity also showed similar association by menopausal status although there was no significant interaction. [20] In contrast, meta-analyses have reported significant positive associations between the DII and breast cancer risk only in postmenopausal women. [1210] Oxidative stress biomarkers have been positively associated with postmenopausal breast cancer and inversely associated with premenopausal breast cancer. [3151] It has been suggested that in premenopausal women oxidative stress may contribute to physiological tumor surveillance and prevention through increased tumor suppressor activity and apoptosis, [5253] whereas in postmenopausal women oxidative stress may result in cumulative genetic damage and carcinogenesis after a long latency period. [54]

There was a stronger association among overweight and obese women, which was consistent with data from the Iowa Women's Health Study. [55] Because obesity is a state of chronic low-grade inflammation, it may elevate breast cancer risk together with pro-inflammatory and pro-oxidant diet. [56] Stronger associations were observed in non-Hispanic Black women and women reporting other race/ethnicity.

The major strengths of our study include a prospective design with a large sample size, low attrition rate, and standardized data collection. Comprehensive information on potential risk factors for breast cancer likely greatly reduced confounding. In addition, we were able to validate D-OBS using oxidative stress biomarkers. Despite its strengths, our study has several limitations. Self-reported FFQ may be subject to measurement error. We expect these errors to be random (i.e., non-differential) with respect to breast cancer risk given the prospective nature of our study and exclusion of cases within one year of FFQ completion, which would tend to bias results towards the null. However, factors such as social desirability could bias dietary intake reporting. If such factors are also related to personality traits that are in turn associated with factors that influence cancer (e.g., acquiescent personality type being associated with immunosuppression), [57] this could bias our results in either direction. Data on these potential biases were not collected in this study.[5859] Further supporting this possibility, it is important to note that the DII scores in the study are generally lower (more anti-inflammatory) than we generally see, on average. [9] This could reflect an impact of social desirability on responses or the generally higher socioeconomic status and possibly greater interest in health than other study populations. As we collected dietary information only at baseline, we could not account for any changes in dietary consumption over time. In addition, only 31 components were available for DII calculation out of a possible 45 food parameters. There was no validation study for the E-DII comprising the specific 31 components that we used. However, there was a validation study using 32 food parameters, including the 31 that we included. [29] Therefore it is highly likely that our E-DII using 31 food parameters is associated with the inflammatory markers used in the validation study. Furthermore, in another US population, there was no significant decrease in predictive ability of the DII in calculations using <30 parameters vs 44 parameters. [28] Another limitation is that there is the possibility of some false positive results due to the small sample size and large number of tests we conducted, including analyses by ER status and in relation to TNBC.

In summary, findings from this nationwide prospective cohort study suggest that compared to women who consume anti-inflammatory and anti-oxidant diets, women whose diets are both pro-inflammatory and pro-oxidant are at higher risk of breast cancer, especially ER– breast cancer and TNBC. Diets that include high consumption of fruits, vegetables, wholegrains, seafood high in n-3 fatty acids, and nuts and legumes and low consumption of red and processed meats, added sugars, and refined grains might be useful to reduce risk of ER– breast cancer and TNBC. Further investigation is needed to understand the underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

Data used in this analysis may be requested from the Sister Study. See https://sisterstudy.niehs.nih.gov/English/coll-data.htm for information on requesting Sister Study data. Other data are available from the corresponding author upon request.

List of abbreviations:

8-iso-PGF$_{2\alpha}$	8-iso-prostaglandin F$_{2\alpha}$
8-iso-PGF$_{2\alpha}$-M	8-iso-prostaglandin F$_{2\alpha}$ metabolite
BMI	body mass index
CIs	confidence intervals
CRP	C-reactive protein
DII	dietary inflammatory index
D-OBS	dietary oxidative balance score
ER	estrogen receptor
FFQ	food frequency questionnaire
HEI-2015	Healthy Eating Index-2015
HER2	human epidermal growth factor receptor-2
HRs	hazard ratios
NSAIDs	nonsteroidal anti-inflammatory drugs
PR	progesterone receptor
SD	standard deviation
TNBC	triple-negative breast cancer

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Novelty and Impact:

Inflammation and oxidative stress may promote breast and other cancers. The role of diet is still uncertain, however. In this study, using the Dietary Inflammatory Index (DII®) and dietary oxidative-balance scores (D-OBS), the authors found that diet may indeed be associated with an increased risk of both overall and especially triple-negative breast cancer. The greatest risk was seen in diets with the poorest pro-inflammatory and pro-oxidative scores combined. These results suggest that modifying dietary lifestyle factors may help reduce the risk of breast cancer.

Table 1.

General characteristics at baseline by quartiles of the dietary inflammatory index and dietary oxidative balance score: The Sister Study 2003–2009

	Dietary inflammatory index								Dietary oxidative balance score							
	Quartile 1		Quartile 2		Quartile 3		Quartile 4		Quartile 1		Quartile 2		Quartile 3		Quartile 4	
Characteristic	< −4.559		−4.559 to −3.556		−3.556 to −1.948		≥ −1.948		< 21		21 to 26		27 to 31		≥ 32	
N	10,890		10,891		10,891		10,891		10,689		11,476		10,724		10,674	
Mean (SD)																
Age at baseline, years	58.2	(8)	56.7	(9)	54.8	(9)	52.1	(9)	51.9	(9)	54.5	(9)	56.5	(9)	59.0	(8)
BMI, kg/m^2	26.1	(5)	27.3	(6)	27.9	(6)	28.8	(6)	28.3	(6)	27.7	(6)	27.3	(6)	26.8	(5)
Total MET-hours of physical activity/week	56.4	(32)	52.1	(31)	49.5	(30)	45.7	(30)	45.8	(29)	49.3	(30)	53.0	(32)	55.7	(32)
Lifetime duration of breastfeeding, weeks [a]	68.4	(73)	66.8	(73)	67.0	(74)	60.4	(70)	59.0	(68)	67.2	(74)	67.1	(72)	69.1	(75)
Age at menopause, years [b]	49.9	(6)	49.8	(6)	49.2	(6)	48.0	(7)	48.1	(7)	49.2	(6)	49.7	(6)	50.0	(6)
Total energy intake (kcal/day)	1551	(509)	1576	(530)	1633	(567)	1676	(618)	1632	(599)	1651	(572)	1600	(543)	1550	(514)
Proportion (%)																
Race/ethnicity																
Non-Hispanic White	88.6		87.5		85.1		78.9		79.5		84.4		87.0		89.3	
Non-Hispanic Black	6.1		6.8		7.7		10.9		10.9		8.2		6.9		5.6	
Other than White or Black	5.3		5.7		7.2		10.2		9.6		7.4		6.2		5.1	
Educational attainment																
High school degree or less	11.2		13.6		15.5		19.9		19.3		14.7		14.0		12.1	
Some college	29.2		31.7		34.6		37.5		37.1		34.0		30.9		31.1	
College degree or higher	59.7		54.8		49.9		42.6		43.7		51.3		55.1		56.8	
Alcohol consumption																
Never	4.1		3.6		3.5		3.6		3.1		3.4		3.8		4.4	
Former	15.5		13.6		14.3		15.4		13.3		13.9		14.1		17.5	
Current drinker, < 1 drink/day	64.8		69.7		69.8		67.5		64.1		67.4		69.4		70.9	
Current drinker, 1–1.9 drink/day	10.5		8.6		8.2		8.1		11.8		9.6		8.7		5.2	
Current drinker, ≥ 2 drink/day	5.2		4.6		4.3		5.4		7.7		5.7		3.9		2.0	
Smoking status																

	Dietary inflammatory index								Dietary oxidative balance score							
	Quartile 1		Quartile 2		Quartile 3		Quartile 4		Quartile 1		Quartile 2		Quartile 3		Quartile 4	
Never	57.2		57.9		57.8		55.2		54.0		57.1		57.9		59.1	
< 10 and > 0 pack-years	23.8		22.5		21.4		20.1		20.7		22.3		22.1		22.6	
< 20 and ≥ 10 pack-years	8.9		8.9		8.7		9.5		10.2		9.0		8.8		8.2	
≥ 20 pack-years	10.1		10.8		12.1		15.2		15.2		11.7		11.3		10.1	
Recent mammogram screening																
<1 y	85.1		83.5		80.0		75.3		75.6		80.1		83.2		84.9	
1 – 2 years	12.2		13.0		15.2		17.8		17.5		14.8		13.3		12.4	
> 2 years or never had a mammogram	2.8		3.5		4.9		7.0		6.9		5.1		3.5		2.7	
Age at menarche ≤ 11 years	19.8		19.8		19.2		19.0		18.6		19.1		19.6		20.5	
Ever use of hormonal birth control	83.8		85.9		85.8		86.7		87.5		86.8		85.2		82.8	
Use of hormone therapy																
None	48.3		53.7		60.1		69.0		69.4		61.2		53.7		46.5	
Estrogen only	22.3		20.6		18.3		16.1		15.2		17.7		20.8		23.7	
Progesterone or combination therapy	29.4		25.7		21.6		15.0		15.5		21.0		25.5		29.9	
1+ first-degree relatives diagnosed with breast cancer before age 50	51.5		55.0		58.7		64.1		64.4		59.5		55.5		49.8	
Postmenopausal	75.8		69.2		62.4		51.3		50.3		60.7		69.4		78.7	

Data are presented as mean (standard deviation), or percentage.

[a] Among women who ever breastfed (n=25,024).

[b] Among postmenopausal women (n=28,172).

Abbreviation: BMI, body mass index; MET, metabolic equivalent; SD, standard deviation.

Table 2.

Association between dietary oxidative balance score (D-OBS) and urinary 8-iso-prostaglandin F2α (8-iso-PGF2α) and its metabolite (8-iso-PGF2α-M) concentrations (ng/mL) in a sample of premenopausal and postmenopausal participants

		8-iso-PGF2α				**8-iso-PGF2α metabolite**			
	D-OBS *	aGM	95% CI			aGM	95% CI		
Pre-menopausal women (n=884)	Quartile 1 (<21)	1.57	(1.46	1.67)		0.78	(0.74	0.82)	
	Quartile 2 (21 to 26)	1.52	(1.43	1.61)		0.74	(0.71	0.78)	
	Quartile 3 (27 to 30)	1.42	(1.32	1.51)		0.69	(0.66	0.73)	
	Quartile 4 (≥ 31)	1.25	(1.17	1.34)		0.64	(0.60	0.67)	
		Beta	95% CI		P	Beta	95% CI		P
	Quartile 1 (<21)	0				0			
	Quartile 2 (21 to 26)	−0.031	(−0.121	0.059)	0.50	−0.046	(−0.116	0.024)	0.2
	Quartile 3 (27 to 30)	−0.100	(−0.197	−0.003)	0.04	−0.116	(−0.191	−0.040)	0.003
	Quartile 4 (≥ 31)	−0.224	(−0.322	−0.126)	<0.001	−0.201	(−0.278	−0.125)	<0.001
	P trend				**<0.001**				**<0.001**
	D-OBS *	aGM	95% CI			aGM	95% CI		
Post-menopausal women (n=519)	Quartile 1 (<21)	0.81	(0.73	0.91)		4.89	(4.30	5.57)	
	Quartile 2 (21 to 26)	0.65	(0.59	0.72)		3.97	(3.52	4.47)	
	Quartile 3 (27 to 30)	0.72	(0.65	0.80)		4.05	(3.60	4.56)	
	Quartile 4 (≥ 31)	0.61	(0.55	0.68)		3.48	(3.07	3.95)	
		Beta	95% CI		P	Beta	95% CI		P
	Quartile 1 (<21)	0				0			
	Quartile 2 (21 to 26)	−0.225	(−0.381	−0.068)	0.01	−0.210	(−0.386	−0.033)	0.02
	Quartile 3 (27 to 30)	−0.119	(−0.279	0.042)	0.15	−0.189	(−0.369	−0.009)	0.04
	Quartile 4 (≥ 31)	−0.290	(−0.456	−0.125)	<0.001	−0.339	(−0.527	−0.151)	<0.001
	P trend				**0.001**				**0.001**

Gas chromatography/ negative ion chemical ionization mass spectrometry (GC/MS) was used for measuring samples from premenopausal participants and liquid chromatography/ negative ion chemical ionization mass spectrometry (LC/MS) was used for measuring samples from postmenopausal participants.

Adjusted for age at baseline urine sampling, race/ethnicity (non-Hispanic White, non-Hispanic Black, or other than White or Black), educational attainment (high school degree or less, some college, or college degree or higher), body mass index (BMI, continuous), leisure-time physical activity (MET-hours/week, quintiles), smoking status (≥20 pack-years, <20 and ≥10 pack-years, <10 and >0 pack-years,

or never smoker), hormone therapy (none, estrogen only, or both estrogen and progesterone), use of aspirin (never, tertiles of lifetime cumulative doses, or missing), use of non-aspirin NSAIDS (never, tertiles of lifetime cumulative doses, or missing) and urinary creatinine.

Geometric mean and 95% CI were calculated on the basis of natural logarithm of 8-iso-PGF2α and 8-iso-PGF2α-M.

Beta and 95% CI were calculated using generalized linear regression.

Abbreviation: aGMD, adjusted geometric mean; D-OBS, dietary oxidative balance score.

*Higher D-OBS indicates a predominance of anti-oxidant exposure.

Table 3.

Association between dietary inflammatory index, dietary oxidative balance score, and risk of breast cancer

			Index score quartiles				P for trend	Continuous 1 SD increment
			Quartile 1	Quartile 2	Quartile 3	Quartile 4		
		Person-years	92605	92278	91571	89960		366414
Dietary inflammatory index	**Total breast cancer**	No. of cases	692	663	648	616		2619
		Model 1, HR (95%CI)[1]	1 (ref)	0.99 (0.88–1.10)	1.01 (0.90–1.12)	1.02 (0.91–1.14)	0.37	1.00 (0.96–1.05)
		Model 2, HR (95%CI)[2]	1 (ref)	0.98 (0.88–1.09)	0.99 (0.89–1.11)	1.01 (0.90–1.13)	0.80	1.00 (0.96–1.04)
	ER+ breast cancer	No. of cases	534	509	497	421		1961
		Model 1, HR (95%CI)[1]	1 (ref)	0.99 (0.87–1.11)	1.01 (0.89–1.14)	0.91 (0.80–1.04)	0.60	0.96 (0.92–1.01)
		Model 2, HR (95%CI)[2]	1 (ref)	0.98 (0.87–1.11)	1.00 (0.89–1.14)	0.93 (0.81–1.07)	0.64	0.97 (0.92–1.02)
	ER − breast cancer	No. of cases	78	88	77	88		331
		Model 1, HR (95%CI)[1]	1 (ref)	1.15 (0.84–1.56)	1.03 (0.75–1.42)	1.24 (0.90–1.71)*	0.37	1.07 (0.96–1.19)
		Model 2, HR (95%CI)[2]	1 (ref)	1.15 (0.85–1.56)	1.05 (0.76–1.44)	1.30 (0.94–1.79)*	0.30	1.09 (0.97–1.22)
	Triple − breast cancer	No. of cases	39	44	44	55		182
		Model 1, HR (95%CI)[1]	1 (ref)	1.14 (0.74–1.75)	1.17 (0.75–1.80)	1.49 (0.97–2.30)	0.27	1.17 (1.02–1.35)
		Model 2, HR (95%CI)[2]	1 (ref)	1.14 (0.74–1.75)	1.17 (0.76–1.80)	1.53 (0.99–2.35)	0.26	1.18 (1.03–1.36)
			Quartile 1	Quartile 2	Quartile 3	Quartile 4		
		Person-years	87843	96201	90774	91596		366414
Dietary oxidative balance score	**Total breast cancer**	No. of cases	611	677	666	665		2619
		Model 1, HR (95%CI)[1]	1 (ref)	0.96 (0.86–1.07)	0.97 (0.87–1.08)	0.91 (0.81–1.03)	0.23	0.97 (0.93–1.01)
		Model 2, HR (95%CI)[2]	1 (ref)	0.96 (0.86–1.07)	0.97 (0.86–1.08)	0.92 (0.81–1.03)	0.23	0.97 (0.93–1.01)
	ER+ breast cancer	No. of cases	428	516	511	506		1961
		Model 1, HR (95%CI)[1]	1 (ref)	1.05 (0.92–1.19)	1.06 (0.93–1.21)	0.99 (0.86–1.13)	0.68	0.99 (0.95–1.04)
		Model 2, HR (95%CI)[2]	1 (ref)	1.03 (0.90–1.17)	1.03 (0.90–1.18)	0.96 (0.83–1.10)	0.98	0.98 (0.94–1.03)
	ER − breast cancer	No. of cases	82	77	85	87		331

			Index score quartiles				P for trend	Continuous 1 SD increment
		Model 1, HR (95%CI)[1]	1 (ref)	0.83 (0.60–1.14)	0.95 (0.70–1.30)	0.95 (0.69–1.31)	0.54	0.99 (0.88–1.11)
		Model 2, HR (95%CI)[2]	1 (ref)	0.82 (0.60–1.12)	0.93 (0.68–1.27)	0.93 (0.67–1.28)	0.43	0.98 (0.87–1.09)
	Triple − breast cancer	No. of cases	51	46	44	41		182
		Model 1, HR (95%CI)[1]	1 (ref)	0.81 (0.54–1.21)	0.81 (0.54–1.23)	0.74 (0.48–1.15)	0.16	0.88 (0.76–1.02)
		Model 2, HR (95%CI)[2]	1 (ref)	0.81 (0.54–1.21)	0.81 (0.54–1.22)	0.74 (0.48–1.15)	0.15	0.88 (0.76–1.02)

[1]Adjusted for age (age as the primary time scale)

[2]Adjusted for race/ethnicity (non-Hispanic White, non-Hispanic Black, or other than White or Black), educational attainment (high school degree or less, some college, or college degree or higher), baseline menopausal status (binary), body mass index (BMI, continuous), interaction term between baseline menopausal status and BMI, physical activity (MET-hours/week, quintiles), smoking status (≥20 pack-years, <20 and ≥10 pack-years, <10 and >0 pack-years, or never smoker), ever use of hormonal birth control, hormone therapy (none, estrogen only, or both estrogen and progesterone), recent mammogram screening (<1, 1–2, or > 2 years or never had a mammogram), number of first-degree relatives diagnosed with breast cancer before age 50 years (0, 1, or ≥2), use of aspirin (never, tertiles of lifetime cumulative doses, or missing), and use of non-aspirin NSAIDS (never, tertiles of lifetime cumulative doses, or missing).

*HR for ER− breast cancer was significantly different from ER+ breast cancer in case–case analysis (P<0.05).

Abbreviation: SD, standard deviation; HR, hazard ratio; 95% CI, 95% confidence interval; ER, estrogen receptor; +, positive; −, negative.

Table 4.

Association between the combination of dietary inflammatory index and dietary oxidative balance score and risk of breast cancer

		Anti-inflammatory and anti-oxidative diet	Either	Pro-inflammatory and pro-oxidative diet
	Person-years	88150	186407	91857
Total breast cancer	No. of cases	615	1365	639
	Model 1, HR (95%CI)[1]	1 (ref)	1.11 (1.01–1.22)	1.13 (1.01–1.27)
	Model 2, HR (95%CI)[2]	1 (ref)	1.10 (1.00–1.21)	1.13 (1.00–1.27)
ER+ breast cancer	No. of cases	473	1047	441
	Model 1, HR (95%CI)[1]	1 (ref)	1.11 (1.00–1.24)	1.03 (0.89–1.17)
	Model 2, HR (95%CI)[2]	1 (ref)	1.11 (0.99–1.24)	1.05 (0.91–1.21)
ER− breast cancer	No. of cases	71	169	91
	Model 1, HR (95%CI)[1]	1 (ref)	1.16 (0.87–1.53)	1.34 (0.96–1.85) *
	Model 2, HR (95%CI)[2]	1 (ref)	1.16 (0.88–1.54)	1.39 (1.00–1.93) *
Triple– breast cancer	No. of cases	34	91	57
	Model 1, HR (95%CI)[1]	1 (ref)	1.29 (0.87–1.93)	1.70 (1.08–2.66)
	Model 2, HR (95%CI)[2]	1 (ref)	1.29 (0.87–1.91)	1.72 (1.10–2.70)

Anti-inflammatory and anti-oxidative diet corresponds to DII tertile 1 & D-OBS tertile 3; Pro-inflammatory and pro-oxidative diet corresponds to DII tertile 3 & D-OBS tertile 1

[1]Adjusted for age (age as the primary time scale)

[2]Adjusted for race/ethnicity (non-Hispanic White, non-Hispanic Black, or other than White or Black), educational attainment (high school degree or less, some college, or college degree or higher), baseline menopausal status (binary), body mass index (BMI, continuous), interaction term between baseline menopausal status and BMI, physical activity (MET-hours/week, quintiles), smoking status (≥20 pack-years, <20 and ≥10 pack-years, <10 and >0 pack-years, or never smoker), ever use of hormonal birth control, hormone therapy (none, estrogen only, or both estrogen and progesterone), recent mammogram screening (<1, 1–2, or > 2 years or never had a mammogram), number of first-degree relatives diagnosed with breast cancer before age 50 years (0, 1, or ≥2), use of aspirin (never, tertiles of lifetime cumulative doses, or missing), and use of non-aspirin NSAIDS (never, tertiles of lifetime cumulative doses, or missing).

*HR for ER- BC was significantly different from ER+ breast cancer in case–case analysis (P<0.05).

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence interval; ER, estrogen receptor; +, positive; −, negative.

Table 5.

Hazard ratios (HRs) and 95% CIs for the association between the combination of dietary inflammatory index and dietary oxidative balance score and risk of breast cancer stratified by selected factors

				Combination of dietary inflammatory index and dietary oxidative balance score			P for interaction
Characteristic		**Person-years**	**No. of cases**	**Anti-inflammatory and anti-oxidative diet**	**Either**	**Pro-inflammatory and pro-oxidative diet**	
Time varying menopausal status	Premenopausal	32299	443	1 (ref)	0.69 (0.53–0.91)	0.65 (0.49–0.87)	0.001
	Postmenopausal	64314	2172	1 (ref)	1.15 (1.03–1.27)	1.20 (1.05–1.37)	
Race/ethnicity	Non-Hispanic White	316583	2281	1 (ref)	1.08 (0.97–1.19)	1.07 (0.94–1.22)	0.23
	Non-Hispanic Black	25916	175	1 (ref)	1.26 (0.81–1.97)	1.41 (0.87–2.30)	
	Other than White or Black	23915	158	1 (ref)	1.38 (0.84–2.27)	1.73 (1.01–2.97)	
No. of first-degree relatives diagnosed with breast cancer before age 50 years	0	154035	1104	1 (ref)	1.15 (1.00–1.32)	1.07 (0.89–1.29)	0.31
	≥1	212379	1510	1 (ref)	1.06 (0.93–1.21)	1.14 (0.98–1.34)	
Body mass index, kg/m^2	Normal weight (<25 and ≥18.5)	147118	963	1 (ref)	0.98 (0.84–1.14)	0.92 (0.75–1.12)	0.05
	Overweight/obese (≥25)	219296	1651	1 (ref)	1.19 (1.05–1.36)	1.28 (1.10–1.48)	
Physical activity	High*	85659	606	1 (ref)	0.96 (0.80–1.15)	0.96 (0.74–1.25)	0.17
	Low to moderate	280755	2008	1 (ref)	1.17 (1.04–1.32)	1.20 (1.05–1.38)	
Alcohol consumption	Non/ past drinker	300882	2160	1 (ref)	1.27 (1.01–1.60)	1.42 (1.07–1.88)	0.24
	Current drinker	65532	454	1 (ref)	1.06 (0.95–1.18)	1.07 (0.94–1.22)	

Adjusted for covariates used in Table 3 except each stratified variable.

*Total metabolic equivalent 21+ hours/week for leisure-time physical activity, corresponding to 420+ min per week of moderate-intensity physical activity.