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Association between post-cancer diagnosis dietary inflammatory potential and mortality among invasive breast cancer survivors in the Women's Health Initiative

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Abstract

Background—Inflammation is important in chronic disease and can be modulated by dietary exposures. Our aim was to examine whether the inflammatory potential of diet after cancer diagnosis, assessed using the dietary inflammatory index (DII[®]), is associated with all-cause and cause-specific mortality among women diagnosed with invasive breast cancer in the Women's Health Initiative (WHI).

Methods—Our analytical cohort included 2,150 post-menopausal women, aged 50 to 79 years at baseline, who developed invasive breast cancer during follow-up and completed a food frequency questionnaire (FFQ) on average 1.5 years after diagnosis. Women were followed from breast cancer diagnosis until death, or the end of follow up by October 2014. Energy-adjusted DII (E-DII) scores were calculated from food plus supplements using a nutrient-density approach. Cox proportional hazards models were fit to estimate multivariable-adjusted HRs and 95% confidence intervals (CI) for all-cause, breast cancer-specific, and cardiovascular disease (CVD) mortality.

Results—After a median 13.3 years of follow-up, 580 deaths from any cause occurred, including 212 breast cancer deaths and 103 CVD deaths. Lower (i.e., more anti-inflammatory) E-DII scores

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Disclosure of conflict of interest: Dr. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII[™]) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

were associated with a lower risk of CVD mortality ($HR_{Q1VSQ4}=0.44$; 95% CI= 0.24–0.82; P-trend= 0.005), but not with breast cancer-specific mortality ($HR_{Q1VSQ4}=0.96$; 95% CI=0.62–1.49; P-trend=0.96) or all-cause mortality ($HR_{Q1VSQ4}=0.82$; 95% CI=0.63–1.05; P-trend=0.17).

Conclusion—Consuming a more anti-inflammatory diet after breast cancer diagnosis may be a means for reducing risk of death from CVD.

Impact—Survival after invasive breast cancer diagnosis may be improved by consumption of an anti-inflammatory diet.

Introduction

Breast cancer is the most frequently diagnosed cancer among women in the US and ranks second after lung cancer as a cause of cancer death (1). It is estimated that more than 4.5 million female invasive breast cancer survivors will be alive in the US by 2026, which constitutes the largest cancer survivor group (2). As breast cancer survival rates are relatively high (5-year survival rates are 89% for all-stages combined) and have been increasing in recent years due to widespread use of mammography and improvements in treatment (2), breast cancer survivors experience increased risks of postdiagnostic comorbidities such as hypertension, arthritis, chronic pulmonary disease, cardiovascular disease (CVD), and diabetes, which have a significant impact on their overall survival (3–5). Therefore, implementing healthy lifestyle changes, including dietary improvement after cancer diagnosis has the potential to exert a strong influence on breast cancer survival. Research has suggested that a majority of breast cancer survivors are highly motivated to make changes in their diets and supplement use after cancer diagnosis (6, 7).

To inform post-diagnosis dietary recommendations, eight observational studies examined associations between post-diagnostic diet quality as assessed using different dietary patterns and breast cancer survival among women diagnosed with invasive breast cancer. Among these studies, three assessed diet quality from *a posteriori* (i.e. data-driven) dietary patterns (8–10), and five focused on *a priori* (score-based) dietary patterns after a breast cancer diagnosis (11–15), with most finding no association with breast cancer-specific mortality but inverse associations between diet quality and non-breast cancer mortality. In addition, three randomized dietary intervention trials assessed whether healthy dietary intervention among women with breast cancer could improve their breast cancer prognosis and overall survival, but reported inconsistent findings (16–18). One dietary intervention to reduce fat intake observed significantly improved relapse-free survival of breast cancer (16), postmenopausal breast cancer survivors in the Women’s Health Initiative Dietary Modification Trial (WHI-DM) with a low-fat dietary pattern had a significant reduced risk of death after breast cancer compared to the usual diet comparison group (18), while in the third study, adoption of a diet that was very high in vegetables, fruit, and fiber and low in fat did not reduce additional breast cancer events or all-cause mortality (17).

Some dietary indices are limited by the relatively small numbers of dietary components included and the lack of focus on specific biologic pathways related to chronic disease and mortality. Given the important role of inflammation in the pathogenesis of many chronic conditions and outcomes, such as cancer and CVD incidence and death (19–23), a dietary

index that focuses on the inflammatory potential of diet as a whole may be better able to predict mortality among cancer patients compared to others focused solely on specific food items derived from data-driven methods or more general dietary guidelines. Therefore, we undertook an analysis to assess the inflammatory potential of post-diagnosis diet using the literature-derived dietary inflammatory index (DII[®]) (24) and examined its association with all-cause mortality, breast cancer-specific mortality, and CVD mortality among women who were diagnosed post-menopause with invasive breast cancer from the WHI Study.

Materials and Methods

Study population

The WHI was established to explore some of the most common predictors of morbidity and mortality among women who were post-menopause, including cancer, CVD and osteoporotic fractures. Details of the design of the WHI have been described (25–27). Briefly, 161,808 women who were post-menopause aged 50 to 79 years were enrolled between 1993 and 1998 from 40 WHI clinical centers across the US into either one or multiple of three randomized controlled Clinical Trials (CT) (n=68,132) which consisted of hormone replacement therapy (HRT) trial, dietary modification (DM) trial, and calcium and vitamin D supplement (CaD) trial or the Observational Study (OS) (n=93,676). Women were not eligible for either the CT or the OS if they had any medical condition with predicted survival of less than three years, or had active participation in other randomized intervention trials. For the WHI-DM trial, participants were additionally excluded if their diet had less than 32% energy from fat or they were on a diabetic or low-salt diet (26). The primary follow-up of CT and OS was closed in 2005 and the participants who consented were continuously followed up in the WHI Extension Study I (2005–2010) and II (2010–2015). Participants from the WHI-DM and WHI-OS had repeated FFQs during follow-up, which allowed us to assess the post-cancer diagnosis diet. We excluded women diagnosed with breast cancer who were enrolled in the WHI-CaD or the WHI-HRT (n=2,527) because they did not complete follow-up FFQs. We also excluded 2,968 WHI-OS participants who did not complete a FFQ after breast cancer diagnosis, and WHI-DM participants who did not complete a FFQ after breast cancer diagnosis but prior to death. Thus, our study included women from WHI-DM and WHI-OS, who were free of cancer at or before baseline except non-melanoma skin cancer, were diagnosed with invasive breast cancer as a first primary cancer during follow-up, and completed an FFQ after diagnosis (n=2,242; WHI-OS=1,008 and WHI-DM=1,234). Among these, we excluded 86 women (WHI-OS=37; WHI-DM=49) who reported implausible daily energy intake (outside the range of 600–5000 kcals/day), four women who did not contribute follow-up time in the cohort, and two women who did not have data on hormone replacement therapy. A total of 2,150 women were included in the analysis. The WHI protocol was approved by the Institutional Review Boards at the Clinical Coordinating Center (CCC) at the Fred Hutchinson Cancer Research Center (Seattle, WA) and at each of the participating Clinical Centers. All participants provided written informed consent in accordance with the US Common Rule.

Dietary assessment

Diet in the past three months was measured using a self-administered FFQ, adapted from instruments previously used in large-scale dietary intervention studies (28-31). The FFQ consisted of three sections: (1) 120 food or food groups with questions on frequency of intake and portion size; (2) four summary questions related to the usual intake of fruits, vegetables, and added fat to compare with information gathered from the food items; (3) 19 adjustment questions that solicited information on food preparation methods and types of fat added so as to permit more refined calculation of fat intake. For quality control purposes, all adjustment and summary questions, 90% of the foods, and at least one-half of every food group section had to be completed (32). Nutrient intake from the FFQ was calculated by linking to the University of Minnesota Nutrition Coordinating Center food and nutrient database (33). Compared to four 24-h dietary recalls and a 4-day food record within the WHI study, the energy-adjusted correlation coefficient for dietary factors in the WHI FFQ ranged from 0.18 for vitamin B12 to 0.68 for magnesium, with a mean of 0.49 (32).

WHI-OS participants completed the FFQ at baseline and year 3 of follow-up, and WHI-DM participants completed the FFQ at baseline and year 1 of follow-up, and thereafter a random subset of approximately one third of DM participants completed the FFQ each year from year 2 to year 9 (34). For the present analysis, we chose the first FFQ that occurred after participants' diagnoses of invasive breast cancer. The identified FFQ occurred, on average, 1.55 years after breast cancer diagnosis for WHI-DM and 1.48 years for OS participants. Data on dietary supplement use was retrieved from baseline and annual visits for WHI-CT and from year 3 follow-up visits for OS where participants brought in their medications and dietary supplements in their original pill bottles. Similar to the identification of post-cancer diagnosis FFQ, we chose supplement use information reported soonest after participants' diagnoses of invasive breast cancer.

Description of energy-adjusted DII score

The energy-adjusted DII (E-DII) score for each participant was calculated based on the nutrient and food intake derived from the WHI FFQ with linkage to the literature-derived inflammatory effect scores included in the DII, which was developed at the University of South Carolina (24). The details of the development and construct validation of DII have been published previously (24, 35–39). Briefly, a total of 1,943 qualifying peer-reviewed primary research articles published through 2010 on the effect of dietary factors on six inflammatory markers (interleukin (IL)-1 β , IL-4, IL-6, IL-10, tumor necrosis factor- α (TNF α), and C-reactive protein (CRP)) were identified and scored to derive the component-specific inflammatory effect scores for 45 dietary factors (i.e., components of DII), comprising macronutrients and micronutrients as well as some bioactive components (24). Thirteen DII components including ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins were not available from the WHI FFQ; therefore, we used the 32 components available in the WHI FFQ to calculate the E-DII score for our analysis. The majority (75%) of participants took supplements after their breast cancer diagnoses and most nutrients contained in dietary supplements have anti-inflammatory properties (24). In addition, findings from a WHI study reported that multivitamin use was associated with lower breast cancer mortality among

women who were post-menopause and who had invasive breast cancer (40). Therefore, in our study we calculated E-DII score from foods plus supplements as the exposure to reflect overall post-cancer dietary quality with regard to inflammatory potential and examined its association with mortality outcomes. In a DII construct validation study using data from the WHI, the DII score calculated based on food and supplement intake of these 32 components was associated with concentrations of inflammatory markers, including IL-6 and TNF α receptor 2 (36).

The WHI FFQ-derived food and nutrient consumption was adjusted first for total energy per 1000 calories and standardized to an energy-adjusted worldwide representative diet database, which included dietary data from 11 populations across the world to avoid the arbitrary use of raw consumption amounts (24, 41). The energy-adjusted standardized dietary intake was then multiplied by the literature-derived inflammatory effect score for each DII component, and summed across all components to obtain the overall energy-adjusted E-DII score (24). Higher E-DII scores represent more pro-inflammatory diets while lower (i.e., more negative) E-DII scores indicate more anti-inflammatory diets.

Other covariate assessments

Information on age at screening, race/ethnicity, education level, family income level, and hormone use was assessed at baseline using self-administered questionnaires. Energy expenditure from recreational physical activity in MET-hours/week (includes walking, mild, moderate and strenuous physical activity) and smoking status were assessed as part of personal habits using the self-administered questionnaires at baseline for all WHI-OS and WHI-DM participants and updated for the WHI-DM only at years 1, 3, 6, and 9. We chose physical activity and smoking status assessed at baseline in our analysis to ensure consistency in the timing of assessments for the entire study population. Physical activity was categorized to four levels (0 MET-hours/week; 0.1–3 MET-hours/week; 3.1–8.9 MET-hours/week; 9 or more MET-hours/week) (11, 42). Weight and height were measured using standard methods during clinic visits at baseline and annually from years 1 to 9 for the WHI-DM and at baseline and year 3 for the WHI-OS. Baseline, instead of post-cancer diagnosis, weight and height were used to calculate the body mass index (BMI) as weight (kg)/height(m)² due to considerable missing data on post-cancer diagnosis information for OS. We categorized the baseline BMI based on the World Health Organization criteria (43).

Identification and ascertainment of incident breast cancer cases have been described in detail elsewhere (44). Briefly, medical records from participants who self-reported outcomes were reviewed first by local physician adjudicators to assign a diagnosis. Centralized review and coding based on related diagnostic documents were subsequently performed at the Clinical Coordinating Center. Detailed cancer characteristics such as stage, anatomic subsite, diagnosis date, extent of disease (stage, tumor size, laterality), tumor morphology (behavior, grade, histology) and hormone receptor results were recorded using the Surveillance, Epidemiology, and End Results (SEER) coding guidelines (45).

Ascertainment of death

There are three mortality outcomes in our analysis: death from any cause, death from breast cancer, and death from CVD. CVD deaths in WHI included death from definite coronary heart disease (CHD), cerebrovascular diseases, pulmonary embolism, possible CHD, other CVD, and unknown CVD based on ICD-9 codes 390–459 or ICD-10 codes I00-I99. Vital status of participants was updated by contacts during annual clinic visits for CT and through mailings for the OS (25). Autopsy and hospitalization records were used to determine the underlying cause of death. If these were unavailable, death certificates, medical records or other records were used (44). In addition, data linkage with the National Death Index was performed periodically for all WHI participants to identify otherwise unreported deaths and to confirm causes of death (44).

Statistical analysis

To describe demographic, lifestyle and clinical characteristics of our study population, we calculated means and standard errors (SE) for continuous variables and number and frequencies for categorical variables by quartiles of E-DII scores. ANOVA was used to test for differences in continuous variables across E-DII quartiles if variance across E-DII quartiles was homogeneous. Welch test was used if variance was heterogeneous (46). The chi-square test was performed to test for differences in categorical variables.

For each mortality outcome, women were followed from diagnosis of primary invasive breast cancer until death, loss to follow-up, the last NDI search date for the participant, or the end of follow up by October 2014. Cox proportional hazards models, with person-years as the underlying time metric, were fitted to estimate age and energy-adjusted and multivariable-adjusted HRs and 95% confidence intervals (CI) with women in the highest E-DII quartile (most pro-inflammatory scores) as the referent. To account for the time period from breast cancer diagnosis to FFQ completion when no subjects were at risk of death due to our study design, we added a time-dependent covariate in the model to stratify participants' status before and after the post-diagnosis FFQ. The proportional hazard (PH) assumption was examined using the Schoenfeld residual test (47). There was no evidence that the E-DII violated PH assumption. However, in analyses where covariates violated the PH assumption, we fitted an extended Cox proportional hazards model (i.e., stratified by categorical covariate or added a time-dependent covariate, which was formed by the product of time and continuous covariate) (48, 49). To test for linear trend in mortality risk across E-DII scores, a continuous E-DII score was used. In multivariable-adjusted models, we adjusted for WHI study component (WHI-OS, WHI-DM-intervention, WHI-DM-control), family income levels, age group at cancer diagnosis, race/ethnicity, education level, cancer stage, years from cancer diagnosis to FFQ completion, baseline physical activity level, smoking status at baseline, baseline BMI categories, total energy intake per day, estrogen receptor (ER) status, progesterone receptor (PR) status, and HRT usage. Although none of these covariates changed the crude hazard ratio of all-cause mortality by more than 10%, we maintained them in the model because they were considered to be important predictors of survival after breast cancer diagnosis in the WHI (11). Cancer stage and ER/PR status were used as proxy for the currently unavailable cancer treatment data, as breast cancer stage and hormone receptor status may influence types of treatment received (50–52).

Breast cancer hormone receptor status is an important predictor of prognosis, and diet may have differential effects on breast cancer development and overall survival depending on hormone receptor status (53, 54). Thus, we planned *a priori* stratified analysis by ER, PR, and combined ER and PR status on the association between E-DII and all-cause mortality. Given the small number of breast cancer-specific deaths in this study, we did not further stratify analyses of breast cancer-specific mortality by hormone receptor status. Cross products of categorical E-DII and ER status and E-DII and PR status were added into the multivariable-adjusted Cox proportional hazards model separately and the likelihood ratio tests were used to evaluate effect modification. A p-value = 0.10 indicated significant interaction.

In sensitivity analysis, we excluded participants from the WHI-DM-intervention arm because long-term dietary intervention can change an individual's dietary habits. We also restricted our analysis to subjects with an FFQ completed at least one year after their cancer diagnosis because cancer treatment may affect the diets of patients with cancer in the first year. Women excluded from our analyses due to death before they could complete a post-diagnosis FFQ were more likely to consume pro-inflammatory diets than our analytical sample. To evaluate the potential for selection bias, demographic and lifestyle factors and tumor characteristics were compared between our sample and all breast cancer survivors in the WHI using either an independent T-test or a Chi-square test to assess the difference for continuous variables and categorical variables, respectively.

All statistical analyses were conducted using SAS[®] (version 9.4, Cary, NC). All tests were two-sided with p values <0.05 considered to be statistically significant if not otherwise noted.

Results

After a median 13.3 years of follow-up, 580 deaths occurred, including 212 breast cancer deaths and 103 CVD deaths. The other main causes of death included lung cancer, pneumonia, other causes, or unknown causes. As shown in Table 1, compared to women with the most pro-inflammatory diets (i.e., E-DII quartile 4), women consuming more anti-inflammatory diets had lower daily energy intake, higher income and education level, longer survival after cancer diagnoses, were more physically active, had lower BMI at baseline, and were more likely to be enrolled in the WHI-DM-intervention arm, be White/non-Hispanic, or be never or past smokers.

Women consuming the most anti-inflammatory diets compared with the most pro-inflammatory diets had a 56% lower risk of death from CVD based on multivariable Cox proportional hazards model ($HR_{Q1VSQ4}=0.44$; 95% CI= 0.24–0.82) (Table 2). However, no association was observed for E-DII with all-cause mortality ($HR_{Q1VSQ4}=0.82$; 95% CI=0.63–1.05) or with breast cancer specific mortality ($HR_{Q1VSQ4}=0.96$; 95% CI=0.62–1.49) (Table 2). When we excluded women from the WHI-DM-intervention (n=448), the HRs did not change materially (Supplemental Table 1). After we excluded women with post-diagnosis FFQs completed within one year after their diagnoses (n=865), the HRs were similar for all-cause mortality and breast cancer specific mortality but the protective effect of

an anti-inflammatory diet on CVD mortality was attenuated ($HR_{Q1VSQ4}=0.69$; 95% $CI=0.30-1.60$) (Supplemental Table 2), which may be largely due to the small sample size and small number of deaths from CVD in this subsample. Compared to our smaller subset, total breast cancer cases in the WHI were, on average, older at diagnosis and had shorter survival, but major differences in risk factors related to mortality or a pro-inflammatory diet were not observed between these two groups (Supplemental Table 3).

After stratifying by breast cancer hormone receptor status, a 27% lower risk of all-cause mortality was found among ER positive (ER+) breast cancer cases in the lowest E-DII quartile compared to women in the highest quartile ($HR_{Q1VSQ4}=0.73$; 95% $CI=0.54-0.97$) (Table 3). However, there was no association among ER negative (ER-) cases. Modest associations were observed for PR+ and PR- cases comparing the most anti-inflammatory diets to the most pro-inflammatory diets ($HR_{Q1VSQ4}=0.84$; 95% $CI=0.60-1.17$; and $HR_{Q1VSQ4}=0.69$; 95% $CI=0.42-1.14$, respectively). When ER and PR status were combined, lower risk was observed among ER+ and/or PR+ cases, but not among ER- and PR- cases (Table 3).

Discussion

Results from this large prospective study of 2,150 women who were post-menopause and diagnosed with invasive breast cancer suggest that consuming a more anti-inflammatory diet after cancer diagnosis is associated with lower CVD mortality risk, but not with all-cause mortality or breast cancer-specific mortality. In the stratified analyses by breast cancer hormone receptor status, an association between anti-inflammatory diet after cancer diagnosis and lower all-cause mortality was seen in the ER+ breast cancer cases and in the combined ER+ and/or PR+ tumors. To our knowledge, this is the first study to examine a post-cancer diagnosis dietary pattern with respect to inflammatory potential of the diet, as defined by E-DII, and all-cause and cause-specific mortality among women who were diagnosed with breast cancer and post-menopausal.

Similar to our findings, most previous cohort studies have not found better dietary quality after breast cancer diagnosis to be associated with breast cancer-specific mortality but have observed lower risks of non-breast cancer mortality (8, 9, 11, 13–15). In a WHI study that examined post-diagnosis Healthy Eating Index (HEI)-2005 scores, having better post-diagnosis diet quality was associated with a 42% lower risk of death from non-breast cancer causes ($HR_{Q4VSQ1}=0.58$; 95% $CI=0.38-0.87$), but was not associated with breast cancer mortality ($HR_{Q4VSQ1}=0.91$; 95% $CI=0.60-1.40$) after a median follow-up of 9.6 years (11). In the Nurse's Health Study (NHS) with a median of 9.3 years follow-up, better adherence to the Dietary Approaches to Stop Hypertension (DASH) score and the Alternative-HEI-2010 after breast cancer diagnosis was associated with a 28% ($RR_{Q5VSQ1}=0.72$; 95% $CI=0.53-0.99$) and 43% ($RR_{Q5VSQ1}=0.57$; 95% $CI=0.42-0.77$) reduced risk of non-breast cancer mortality, respectively, among women who were, on average, 60 years old at diagnosis. Neither pattern was associated with breast cancer mortality ($RR_{Q5VSQ1}=0.85$; 95% $CI=0.61-1.19$ for DASH; and $RR_{Q5VSQ1}=1.07$; 95% $CI=0.77-1.49$ for AHEI-2010), and no significant effect modification by ER status was observed for either pattern (13). Results from another NHS study reported better adherence to four *a priori* dietary indices

after breast cancer diagnosis, including AHEI, Diet Quality Index-Revised (DQIR), Recommended Food Score (RFS), and the alternate Mediterranean Diet Score (aMED), was not associated with breast cancer mortality (14). Similar results also were observed from two studies which examined *a posteriori* dietary patterns (prudent and Western dietary patterns) after breast cancer diagnosis among women with the majority being postmenopausal at diagnosis (8, 9). One study with median follow-up of 9 years found a 46% (RR Q_5 vs Q_1 = 0.54; 95% CI = 0.31–0.95) lower risk of mortality from other causes than breast cancer in the highest compared to the lowest quintile of a prudent pattern (8), and the other study with a mean follow-up of 4.2 years found a 65% reduced non-breast cancer mortality risk associated with highest adherence to a prudent pattern (HR Q_4 vs Q_1 = 0.35; 95% CI = 0.17–0.73) (9). Anti-inflammatory DII scores were associated with better diet quality scores on other dietary indices including AHEI, DASH and HEI-2010 (55), and CVD is a leading cause of death for older breast cancer survivors (56). Thus, while other studies did not examine CVD mortality specifically, the reduced CVD mortality associated with better dietary quality observed in the present study is likely comparable to, and in agreement with, the lower non-breast cancer mortality risk observed in previous cohort studies (8, 9, 11, 13–15).

Biologically, atherosclerosis, the primary factor inducing CVD, is an inflammatory condition associated with elevated plasma levels of inflammatory cytokines (57, 58). Pro-inflammatory diets represented by higher DII scores have been related to both elevated CVD incidence (59, 60) and mortality risk (61–63). Data also suggest that higher levels of inflammation among patients with inflammatory diseases, such as polyarthritis, increases CVD mortality (58). However, one recent study using data from the Cancer Prevention Study-II Nutrition Cohort found contrasting findings, and reported after a mean follow-up time of 9.9 years, post-diagnostic diets consistent with the American Cancer Society recommendations for cancer prevention were not associated with CVD mortality among 4,452 breast cancer survivors whose mean age at diagnosis was 70 years (15). The difference compared to our findings in part may be explained by the different dietary patterns evaluated with perhaps diet-associated inflammation being a more important contributor to risk of CVD mortality than diets adhering to cancer prevention guidelines.

The null association we found for breast cancer-specific mortality was largely consistent with previous studies (8, 9, 11, 13, 14). It has been suggested that U-shaped rather than linear associations of several key dietary factors may better represent associations with breast cancer survival (64). However, in our previous study with 122,788 postmenopausal women in the WHI without prior cancer, a higher risk of death from breast cancer was associated with consumption of more pro-inflammatory diets at baseline (HR Q_5 vs Q_1 = 1.33; 95% CI = 1.01–1.76) (65). There is little evidence regarding the association between diet-associated inflammation after breast cancer diagnosis and breast cancer survival. Therefore, future cohort studies are warranted to examine if post-diagnosis inflammatory potential of diet influences cancer survival among those who already have cancer.

Results from the Women's Healthy Eating and Living (WHEL) randomized controlled trial suggested that adoption of a healthy diet high in vegetables, fruit, and fiber and low in fat (also likely to be anti-inflammatory) did not reduce all-cause mortality among 3,088 women

previously treated for early-stage breast cancer (HR=0.91; 95% CI=0.72–1.15) (17). However, some observational studies have reported inverse associations for post-diagnosis diet quality and all-cause mortality, including the WHI (9–12). In the WHI-DM trial, women randomized to the diet characterized by low fat and increased intake of fruits, vegetables, and grains had lower risk of death after breast cancer compared to the usual diet comparison group (HR=0.82; 95% CI=0.70–0.96) (18). The lack of a substantial association observed for all-cause mortality in the present study may reflect the sum effect of mixed associations of E-DII with risk of death from different disease outcomes.

Stratified analysis showed that a lower all-cause mortality risk was seen among ER+ breast cancer cases and among the combined ER+ and/or PR+ cases but not ER-/PR- cases. Our results were similar to another WHI study which found an inverse relationship between post-diagnosis HEI-2005 score and all-cause mortality among ER+ women (HR_{Q4VSQ1}=0.55; 95% CI=0.38–0.79, P-trend=0.0009) but not among those with ER- tumors (HR_{Q4VSQ1}=1.14; 95% CI, 0.58–2.23, P-trend=0.81) (11). It is suggested that women diagnosed with ER+ cancers generally have better prognosis than ER- cancers (66), and thus they are more likely to die of CVD, a leading cause of death among older breast cancer survivors (56). This may partially explain our observed stronger association among ER+ tumors given the significant association between E-DII and CVD mortality we identified in this study. As a result of small sample size in the ER+ tumors and ER+ and/or PR+ tumors, the stronger association seen among women with ER+ and or PR+ tumors also may be due to chance. Future studies with sufficient sample size examining association between post-diagnosis diet quality and mortality by breast cancer subtypes are warranted.

Strengths of our study include the use of the E-DII which was specifically designed to assess inflammatory potential of diet while accounting for energy intake differences among individuals and can be applied to diverse populations. Other advantages include a large and well-characterized study population, the prospective nature of the study with a long follow-up to allow for accruing a large number of events, and inclusion of important covariates for adjustment. Detailed adjudication of cause of death minimized misclassification of outcomes. We conducted sensitivity analyses to rule out potential bias resulting from the effect of WHI dietary intervention and cancer treatment on post-diagnosis diet habits.

Limitations of our study included measurement error in using the WHI FFQ for dietary assessment (32), which is unavoidable with any dietary assessment tool (67). Diet and supplement use were assessed only at one time point after cancer diagnosis in our study though they may change during the long study follow-up. The longitudinal stability of DII scores was investigated in the WHI-OS and DM control arm participants, and DII scores did not change significantly over time (68). Although we did not detect significant differences on important indicators related to pro-inflammatory diet or death, women who were excluded from our subset were older at diagnosis and had worse survival than included participants. Because we required a post-diagnosis FFQ, it is conceivable that women who had strongly pro-inflammatory diets developed more aggressive tumors and died before they could complete a post-diagnosis FFQ (65). In addition, 13 dietary components of the DII were not available from the WHI FFQ. All of these 13 missing components are anti-inflammatory and some may have a beneficial effect on breast cancer survival (69).

However, as previously reported, the range of DII scores may rely more on the amount of foods actually consumed rather than on the number of available DII components (65). Any misclassification in dietary inflammatory potential due to the missing dietary factors would likely be non-differential, and subsequently attenuate results toward the null. Inflammatory effect scores for each component of the E-DII were developed based on a comprehensive review of the literature reporting each component's association with six inflammatory biomarkers. However, the absence of an established biomarker of energy-adjusted dietary inflammatory potential implies uncertainty concerning the properties of the corresponding E-DII assessment. Additionally, there may be other inflammatory biomarkers beyond the six originally included in the development of the DII that are relevant to breast cancer survival, such as serum amyloid A (SAA) (70). However, the literature relating dietary factors to SAA is limited at this time, so inclusion of SAA in the construction of the DII is unlikely to change the scoring substantially. Although we adjusted for a large number of potential confounders, residual or unmeasured confounding may still be a possibility. In addition, as we did not have data on treatment, we used cancer stage and ER/PR status as proxy. Given the small sample size and small number of deaths in the sensitivity analyses and stratified analysis by ER and PR status, we cannot rule out that findings of these analyses were due to chance. Finally, our sample included only women who were post-menopausal. Future research on this topic should include large cohort studies with adequate treatment data and among younger women diagnosed with breast cancer.

In summary, in this large prospective study of women who were post-menopausal and diagnosed with invasive breast cancer, diet and supplement use with more anti-inflammatory potential after breast cancer diagnosis, as defined by lower E-DII scores, was associated with lower risk of death from CVD but not with breast cancer-specific or all-cause mortality. Our findings suggest that lowering the inflammatory potential of diet after cancer diagnosis may be important in reducing the risk of death from CVD among breast cancer survivors. Future large cohort studies are warranted to explore whether post-diagnosis inflammatory diet might affect outcomes in other cancers or affect survival in breast cancer survivors by specific subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic, lifestyle and clinical characteristics of 2,150 postmenopausal women diagnosed with invasive breast cancer in the WHI-DM and WHI-OS by quartile of E-DII

	Most anti-inflammatory diet				Most pro-inflammatory diet				P ^a
	E-DII Quartile 1 (-6.81, -4.49)	E-DII Quartile 2 (-4.48, -3.46)	E-DII Quartile 3 (-3.45, -2.01)	E-DII Quartile 4 (-2.00, 3.79)	E-DII Quartile 1 (-6.81, -4.49)	E-DII Quartile 2 (-4.48, -3.46)	E-DII Quartile 3 (-3.45, -2.01)	E-DII Quartile 4 (-2.00, 3.79)	
Number of subjects	538	537	538	537	538	537	538	537	
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Age at breast cancer diagnosis (years)	65.6 (0.3)	66.4 (0.3)	66.6 (0.3)	66.6 (0.3)	66.6 (0.3)	66.6 (0.3)	66.3 (0.3)	66.3 (0.3)	0.08
Years from breast cancer diagnosis to FFQ	1.5 (0.05)	1.5 (0.05)	1.6 (0.05)	1.6 (0.05)	1.6 (0.05)	1.6 (0.05)	1.5 (0.05)	1.5 (0.05)	0.57
Years from breast cancer diagnosis to death from any cause	8.4 (0.3)	8.1 (0.3)	8.4 (0.3)	8.1 (0.3)	7.5 (0.3)	7.5 (0.3)	7.3 (0.3)	7.3 (0.3)	0.03
Total energy intake after cancer diagnosis (kcal/day)	1366.7 (18.5)	1506.2 (20.5)	1631.1 (25.7)	1631.1 (25.7)	1631.1 (25.7)	1631.1 (25.7)	1665.4 (28.4)	1665.4 (28.4)	<0001
BMI at enrollment (kg/m ²)	27.0 (0.3)	27.7 (0.3)	28.5 (0.2)	28.5 (0.2)	28.5 (0.2)	28.5 (0.2)	29.6 (0.3)	29.6 (0.3)	<0001
Physical activity at enrollment in MET- hours/week	15.5 (0.7)	13.2 (0.6)	10.4 (0.5)	10.4 (0.5)	10.4 (0.5)	10.4 (0.5)	8.7 (0.5)	8.7 (0.5)	<0001
	N(%) ^b	N(%) ^b	N(%) ^b	N(%) ^b	N(%) ^b	N(%) ^b	N(%) ^b	N(%) ^b	
WHI components									<0001
WHI OS	285 (53.0)	258 (48.0)	220 (40.9)	220 (40.9)	220 (40.9)	220 (40.9)	205 (38.2)	205 (38.2)	
WHI DM-intervention	134 (24.9)	122 (22.8)	116 (21.6)	116 (21.6)	116 (21.6)	116 (21.6)	76 (14.1)	76 (14.1)	
WHI DM-control	119 (22.1)	157 (29.2)	202 (37.5)	202 (37.5)	202 (37.5)	202 (37.5)	256 (47.7)	256 (47.7)	
Race/Ethnicity									<0001
White non-Hispanic	482 (89.6)	498 (92.7)	475 (88.3)	475 (88.3)	475 (88.3)	475 (88.3)	448 (83.4)	448 (83.4)	
Hispanic/Latino	11 (2.0)	11 (2.1)	15 (2.8)	15 (2.8)	15 (2.8)	15 (2.8)	16 (3.0)	16 (3.0)	
Black/African-American	19 (3.5)	17 (3.2)	26 (4.8)	26 (4.8)	26 (4.8)	26 (4.8)	56 (10.4)	56 (10.4)	
Other	26 (4.8)	11 (2.0)	22 (4.1)	22 (4.1)	22 (4.1)	22 (4.1)	17 (3.2)	17 (3.2)	
Income level									<0001
<20,000	45 (8.4)	45 (8.4)	76 (14.1)	76 (14.1)	76 (14.1)	76 (14.1)	89 (16.6)	89 (16.6)	
20,000-49,999	209 (38.8)	252 (46.9)	215 (40.0)	215 (40.0)	215 (40.0)	215 (40.0)	241 (44.9)	241 (44.9)	
>=50,000	257 (47.8)	216 (40.2)	218 (40.5)	218 (40.5)	218 (40.5)	218 (40.5)	170 (31.7)	170 (31.7)	
missing	27 (5.0)	24 (4.5)	29 (5.4)	29 (5.4)	29 (5.4)	29 (5.4)	37 (6.9)	37 (6.9)	
Education level									<0001
High school or below	105 (19.5)	120 (22.3)	140 (26.0)	140 (26.0)	140 (26.0)	140 (26.0)	178 (33.0)	178 (33.0)	

	Most anti-inflammatory diet				<i>P</i> ^a
	E-DII Quartile 1 (-6.81, -4.49)	E-DII Quartile 2 (-4.48, -3.46)	E-DII Quartile 3 (-3.45, -2.01)	E-DII Quartile 4 (-2.00, 3.79)	
Some college	144 (26.8)	149 (27.8)	159 (29.5)	167 (31.0)	
College	72 (13.4)	77 (14.3)	74 (13.7)	51 (9.5)	
Post graduate	213 (39.6)	187 (34.8)	163 (30.2)	137 (25.4)	
Missing	4 (0.7)	4 (0.7)	3 (0.6)	6 (1.1)	
Cancer stage					0.36
Localized	416 (77.3)	403 (75.0)	394 (73.2)	393 (73.2)	
Regional	114 (21.2)	127 (23.7)	130 (24.2)	137 (25.5)	
Distant	4 (0.7)	4 (0.7)	4 (0.7)	4 (0.7)	
Unknown	4 (0.7)	3 (0.6)	10 (1.9)	3 (0.6)	
Smoking status at enrollment					0.02
Never smoked	228 (42.4)	281 (52.3)	266 (49.4)	261 (48.6)	
Past smoker	269 (50.0)	230 (42.8)	239 (44.4)	229 (42.6)	
Current smoker	28 (5.2)	20 (3.7)	25 (4.7)	39 (7.3)	
Missing	13 (2.4)	6 (1.1)	8 (1.5)	8 (1.5)	
Estrogen receptor status					0.12
Positive	429 (79.7)	400 (74.5)	411 (76.4)	391 (72.8)	
Negative	63 (11.7)	74 (13.8)	71 (13.2)	91 (17.0)	
Others ^c	46 (8.6)	63 (11.7)	56 (10.4)	55 (10.2)	
Progesterone receptor status					0.21
Positive	351 (65.2)	321 (59.8)	350 (65.1)	317 (59.0)	
Negative	125 (23.2)	143 (26.6)	125 (23.2)	153 (28.5)	
Others ^d	62 (11.5)	73 (13.6)	63 (11.7)	67 (12.5)	

^a*P* value was calculated from ANOVA test for continuous variables and from Chi-Square test for categorical variables.

^bThe sum of percentages in certain E-DII quartile for some categorical variables may not add up to 100% because of rounding.

^cThis category included data from borderline status or missing.

^dThis category included data from borderline status or missing.

Table 2

Association of post-diagnosis E-DII with all-cause mortality, breast cancer-specific mortality and CVD mortality among 2,150 women diagnosed with invasive breast cancer in the WHI-DM and OS

	Most anti-inflammatory diet				Most pro-inflammatory diet		P_{trend}^d
	E-DII score quartile 1 (-6.81, -4.49)	E-DII score quartile 2 (-4.48, -3.46)	E-DII score quartile 3 (-3.45, -2.01)	E-DII score quartile 4 (-2.00, 3.79)			
N	538	537	538	537	537	537	
Death from any cause (n)	130	148	141	141	161	161	
Age and energy - adjusted HR (95% CI)	0.67 (0.53-0.85)	0.81 (0.65-1.01)	0.77 (0.62-0.97)	0.77 (0.62-0.97)	1.00 (referent)	1.00 (referent)	0.0003
Multivariable adjusted HR (95% CI) ^b	0.82 (0.63-1.05)	0.96 (0.76-1.22)	0.86 (0.68-1.08)	0.86 (0.68-1.08)	1.00 (referent)	1.00 (referent)	0.17
Death from breast cancer (n)	46	58	57	57	51	51	
Age and energy -adjusted HR (95% CI)	0.81 (0.54-1.22)	1.06 (0.73-1.55)	1.09 (0.74-1.59)	1.09 (0.74-1.59)	1.00 (referent)	1.00 (referent)	0.43
Multivariable-adjusted HR (95% CI) ^c	0.96 (0.62-1.49)	1.20 (0.80-1.80)	1.18 (0.80-1.76)	1.18 (0.80-1.76)	1.00 (referent)	1.00 (referent)	0.96
Death from CVD (n)	18	26	26	26	33	33	
Age and energy -adjusted HR (95% CI)	0.44 (0.24-0.78)	0.67 (0.40-1.12)	0.65 (0.39-1.08)	0.65 (0.39-1.08)	1.00 (referent)	1.00 (referent)	0.002
Multivariable-adjusted HR (95% CI) ^d	0.44 (0.24-0.82)	0.69 (0.40-1.20)	0.66 (0.38-1.12)	0.66 (0.38-1.12)	1.00 (referent)	1.00 (referent)	0.005

^a P_{trend} was calculated using the continuous E-DIITM in the COX proportional hazards regression model.

^b Stratified by age group at diagnosis (≤ 66 years old, > 66 years old), estrogen receptor status (positive, negative, others), race/ethnicity (White non-Hispanic, Hispanic/Latino, Black/African-American, other), and progesterone receptor status (positive, negative, others) due to PH assumption violation and was adjusted for WHI component (OS, DM-intervention, DM-control), smoking status at baseline (never smoked, past smoker, current smoker, missing), income levels ($< 20,000$, $20,000-49,999$, $\geq 50,000$, missing), cancer stage (localized, regional, distant, unknown), education (high school or below, some college, college, postgraduate, missing), years from cancer diagnosis to FFQ (continuous), baseline physical activity in MET-h/week (0, 0-3, 3-9, 9+), total energy intake per day (continuous), body mass index at baseline (underweight, normal, overweight, obese, missing), hormone replacement use status at baseline (never used, current user and past user), with the covariate of time-dependent status before and after post-diagnosis FFQ.

^c Stratified by education and progesterone receptor status due to PH assumption violation and adjusted for other covariates listed in ^b.

^d Stratified by estrogen receptor status due to PH assumption violation and adjusted for other covariates listed in ^b.

Risk of all-cause mortality stratified by hormone receptor status of invasive breast cancer across quartiles of post-diagnosis E-DII in the WHI-DM and OS

	Most anti-inflammatory diet			Most pro-inflammatory diet			P_{trend}^a	$P_{\text{interaction}}^b$
	E-DII score quartile 1 (-6.81, -4.49)	E-DII score quartile 2 (-4.48, -3.46)	E-DII score quartile 3 (-3.45, -2.01)	E-DII score quartile 4 (-2.00, 3.79)				
Estrogen receptor status								
ER+; n^c=1,631 cases, n (%)^d	100 (23.3)	113 (28.3)	97 (23.6)	113 (28.9)				
Multivariable-adjusted HR (95% CI)^e	0.73 (0.54-0.97)	0.95 (0.72-1.25)	0.77 (0.58-1.02)	1.00 (referent)			0.04	0.44
ER-; n^c=299 cases, n (%)^d	19 (30.2)	21 (28.4)	31 (43.7)	31 (34.1)				
Multivariable-adjusted HR (95% CI)^e	0.97 (0.49-1.91)	0.63 (0.31-1.25)	1.17 (0.64-2.11)	1.00 (referent)			0.53	
Progesterone receptor status								
PR+; n^c=1,339 cases, n (%)^d	84 (23.9)	85 (26.5)	81 (23.1)	88 (27.8)				
Multivariable-adjusted HR (95% CI)^e	0.84 (0.60-1.17)	0.96 (0.70-1.33)	0.78 (0.57-1.07)	1.00 (referent)			0.08	0.57
PR-; n^c=546 cases, n (%)^d	33 (26.4)	43 (30.1)	44 (35.2)	51 (33.3)				
Multivariable-adjusted HR (95% CI)^e	0.69 (0.42-1.14)	0.86 (0.54-1.39)	0.97 (0.61-1.53)	1.00 (referent)			0.50	
Combined estrogen and progesterone receptor status								
ER+ and/or PR+; n^c= 1,663 cases, n (%)^d	102 (23.4)	116 (28.5)	101 (24.2)	116 (28.8)				
Multivariable-adjusted HR (95% CI)^e	0.77 (0.57-1.02)	0.99 (0.75-1.30)	0.80 (0.60-1.05)	1.00 (referent)			0.05	
ER- and PR-; n^c= 259 cases, n (%)^d	17 (32.1)	18 (27.7)	26 (40.6)	26 (33.8)				
Multivariable-adjusted HR (95% CI)^e	1.09 (0.53-2.24)	0.77 (0.38-1.54)	1.16 (0.62-2.18)	1.00			0.99	

^a P_{trend} was calculated using the continuous E-DIITM in the COX proportional hazards regression model.

^b $P_{\text{interaction}}$ was calculated by adding the cross-product of quartile E-DII and the effect modifier in the COX proportional hazards regression model.

^c The total number of invasive breast cancers with the molecular subtype.

^d Number of deaths from any cause (proportion of deaths from any cause among the total number of invasive breast cancer cases within each quartile).

^e Model was adjusted for age group at diagnosis (<=66 years old, >66 years old), race/ethnicity (White non-Hispanic, Hispanic/Latino, Black/African-American, other), WHI component (OS, DM-intervention, DM-control), smoking status at baseline (never smoked, past smoker, current smoker, missing), income levels (<20,000, 20,000-49,999, >=50,000, missing), cancer stage (localized, regional, distant, unknown), education (high school or below, some college, college, postgraduate, missing), years from cancer diagnosis to FFQ (continuous), baseline physical activity in MET-h/week (0, 0-3, 3-9.9+), total energy intake per day (continuous), body mass index at baseline (underweight, normal, overweight, obese, missing), hormone replacement use status at baseline (never used, current user and past user), with the covariate of time-dependent status before and after post-diagnosis FFQ.