Published in final edited form as:

Breast Cancer Res Treat. 2016 August ; 159(1): 139–149. doi:10.1007/s10549-016-3925-6.

Patterns of change over time and history of the inflammatory potential of diet and risk of breast cancer among postmenopausal women

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Abstract

Purpose—We utilized the dietary inflammatory index (DII) to investigate associations between patterns of change in, and history of the inflammatory potential of diet and risk of breast cancer in the Women’s Health Initiative (WHI).

Methods—We included 70,998 postmenopausal women aged 50–79 years recruited from 1993–1998 into the WHI Observational Study and Dietary Modification trial control group, and followed through August 29, 2014. We utilized data from food frequency questionnaires administered at baseline and Year 3, to calculate average DII scores, and patterns of change in DII, and used these measures in multivariable-adjusted Cox regression models to estimate hazards ratios (HR) and 95% confidence intervals (CI) for incident invasive breast cancer and its subtypes.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

Disclosure: Dr. James R. Hebert 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.

Results—After 1,093,947 person-years of follow-up, 3,471 cases of invasive breast cancer were identified. There was no substantial association between average DII scores or patterns of change in DII and risk of overall invasive breast cancer (HR, 1.03; 95% CI, 0.90, 1.17; $P_{\text{trend}}=0.79$; comparing extreme DII quintiles). However, there was a significant nonlinear association between average DII scores and the ER–, PR–, HER2+, subtype (HR, 2.37; 95% CI, 1.08, 5.20; $P_{\text{trend}}=0.18$; comparing extreme quintiles). For patterns of change in DII, the age-adjusted association with ER–, PR–, HER2+ subtype comparing women in the pro-inflammatory stable to those in the anti-inflammatory stable categories (HR, 1.82; 95%CI, 1.06, 3.13) persisted in the multivariable-adjusted model but was less precise and marginally significant (HR, 1.85; 95%CI, 0.96, 3.55; P -value associated with this HR was 0.06).

Conclusions—Dietary inflammatory potential may differentially influence the development of specific breast cancer phenotypes.

Keywords

breast cancer; dietary patterns; inflammation; diet

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in American women [1] and most of the established risk factors, including reproductive factors, family history of breast cancer, age, BRCA1 and BRCA2 mutations, and breast density [2] are generally non-modifiable. Diet, a potentially modifiable factor has been implicated in breast carcinogenesis, with specific factors such as alcohol [3, 4] and red/processed meat [5] shown to be associated with higher risk. The fact that people eat meals consisting of a wide variety of individual foods with potentially complex interactions among the foods and nutrients has led to a growing interest in the examination of broader dietary patterns in relation to breast cancer risk.

Results of previous prospective cohort studies examining the association between dietary patterns and breast cancer risk are inconsistent. Some have found a higher risk of breast cancer with the Western (or unhealthy) diet pattern [6] or a lower risk with the prudent (or healthy) pattern [7, 8], while others have failed to observe a significant association [reviewed in 9, 10]. Indeed, some studies have found results contrary to hypothesized associations; that is, higher consumption of the prudent pattern associated with higher risk [11] and higher consumption of the Western pattern associated with lower risk [12]. In addition, findings from three large cohort studies have not supported an association between Western or prudent patterns and breast cancer risk [13, 14].

Breast cancer is a heterogeneous disease with multiple intrinsic tumor subtypes [15]. It is therefore important to consider etiologic differences across subtypes. Previous large prospective studies did not find associations between several *a priori* dietary patterns and overall invasive breast cancer risk, however, these studies found significant associations with some tumor subtypes [16, 17], thus suggesting potential heterogeneity by subtype. For example, Fung *et al*, found inverse associations between higher scores on the alternative healthy eating index and alternative Mediterranean dietary pattern and estrogen receptor

negative breast cancer subtype [16], while Hirko *et al* found an inverse association between higher Dietary Approaches to Stop Hypertension scores and HER2 negative subtype [17].

Chronic inflammation is important in the carcinogenesis process [18–20] and has been shown to influence breast cancer development [21, 22]. Therefore, dietary patterns associated with chronic inflammation, as measured by the level of several inflammation markers, may influence breast cancer risk. In addition, intake of unhealthful foods may influence chronic disease risk, including breast cancer risk, when consumed over long periods of time [23]. Therefore changes in diet or a history of dietary intake over time may be more predictive of breast cancer risk compared to diet assessed at one time point. Two previous studies [24, 25] that calculated the dietary inflammatory index (DII) [26] at one time point only, found conflicting results for the association of DII scores with breast cancer risk. The DII is a literature-derived dietary index that assesses diet quality based on its inflammatory potential from maximally anti-inflammatory to maximally pro-inflammatory. In the current study, we utilized the DII to investigate the role of patterns of change as well as history of dietary intake over time in the inflammatory potential of diet on the risk of overall invasive breast cancer and subtypes of breast cancer in postmenopausal women.

METHODS

Study population

The design of the WHI has been described [27]. Briefly, between 1993 and 1998, the WHI enrolled 161,808 women with a predicted survival of >3 years, in 40 sites across the United States, into an Observational Study (OS) (93,676 women) or one or more of three Clinical Trials (CT) (68,132 women). One of the CTs was the Dietary Modification Trial (DM) with 48,885 participants. Women were excluded from the DM if their baseline diets were assessed to have <32% energy intake from fat [28]. For the DM, women were randomly assigned to a usual-diet comparison group (n=29,294) or an intervention group (n=19,541) with a 20% low-fat dietary pattern with increased vegetables, fruits, and whole grains. Women who proved to be ineligible for, or who were unwilling to enroll in, the CT components were invited to be part of the prospective cohort of women in the OS. Follow-up for the WHI is ongoing and we used data from women with follow-up until August 29, 2014 for this investigation [27]. 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 40 clinical centers.

Dietary assessment

At baseline, all WHI participants completed a standardized self-administered 122-item food frequency questionnaire (FFQ) developed for the WHI to estimate average daily nutrient intake over the previous three-month period. Follow-up measures included: an FFQ completed by all DM participants at Year 1; an FFQ completed annually from year 2 until study end (approximately ten years) in a random third of DM participants; and an FFQ completed at Year 3 for ≈90% of OS participants. There was an average of two FFQs per participant in the OS and three FFQs per participant in the DM. Therefore to maximize the number of DM participants with a FFQ at one time point (other than year 1), we created a

composite FFQ for year 3 that included an average of FFQs in years 2, 3 and 4. The composite FFQ was the average number of FFQs administered to participants in years 2, 3, and 4. We did not use FFQs beyond year 4 because the sample sizes of DM participants with FFQs became progressively smaller. Secondly, we did not include baseline FFQ data for DM participants in the analyses due to the upward bias in baseline mean percent energy from fat as a result of the >32% energy from fat eligibility criterion [29–32]. For the current study, we included FFQs from the OS and DM control group but not from the DM intervention group because the intervention group participants were actively undergoing dietary changes while the control group participants were asked to follow their usual diets [28, 31, 33].

FFQ data were considered complete if all adjustment questions (used to capture more complete dietary behavior than food items alone), all summary questions (used to adjust for potential misreporting of individual foods), 90% of the foods, and at least one-half of every food group section was completed [27]. The nutrient database, linked to the University of Minnesota Nutrition Data System for Research (NDSR[®]) [34], is based on the US Department of Agriculture Standard Reference Releases and manufacturer information. The WHI FFQ has produced results comparable to those obtained from four 24-hour dietary recall interviews and four days of food diaries recorded within the WHI [28].

Dietary inflammatory index (DII)

Details of the development [26] and construct validation [35, 36] of the DII have been described. Briefly, an extensive literature search was performed to obtain peer-reviewed journal articles that examined the association between six inflammatory markers (Interleukin (IL)-1 β , IL-4, IL-6, IL-10, tumor necrosis factor alpha, and C-reactive protein) and specific dietary factors. A total of 1,943 eligible articles published through 2010 were indexed and scored to derive inflammatory effect scores for 45 specific nutrients and foods (components of the DII) that were identified in the search. Actual dietary intake data derived from the WHI FFQ were standardized to a representative global diet database constructed based on 11 datasets from diverse populations in different parts of the world. Global mean intake data were used, as opposed to intake data from only one country or geographic region, in order to be able to apply the DII to studies in various countries and regions of the world. The standardized dietary intake data were then multiplied by the literature-derived inflammatory effect scores for each DII component, and summed across all components, to obtain the overall DII [26]. Higher DII scores indicate a more pro-inflammatory diet, and lower (i.e., more negative) scores indicate a more anti-inflammatory diet. In the WHI FFQ, 32 of the 45 original DII components were available for inclusion in the overall DII score. A list of all 45 DII components including the 32 components available in the WHI FFQ is included as a footnote to Table 1.

Outcome assessment

Outcomes included invasive breast cancer and subtypes of invasive breast cancer. As previously described [37], women's self-report of breast cancer was adjudicated by physicians through a review of medical records and pathology reports at each clinical center, with final central adjudication by WHI cancer coders at the CCC. Breast cancer subtypes for the current analysis were defined based on estrogen receptor (ER), progesterone receptor

(PR) and human epidermal growth factor receptor 2 (HER2) status [38], and combined as triple negative (ER–, PR–, HER2–); ER–, PR–, HER2+ subtype, luminal A (ER+ and/or PR+, HER2–); and luminal B (ER+ and/or PR+, HER2+) subtypes [39]. The histological subtypes were defined based on Surveillance Epidemiology and End Results (SEER) program morphology codes. These included invasive ductal carcinoma (8500/3), and invasive lobular carcinoma (8520/2). *In situ* breast cancer cases were not included. Time to invasive breast cancer was defined as days from enrollment or randomization until invasive breast cancer diagnosis, while censoring time was defined as days from enrollment or randomization until death or last contact occurring on or before August 29, 2014, in participants without breast cancer.

Statistical analysis

We utilized data from 122,970 women participating in the WHI OS (n=93,676) and DM control group (n=29,294). Exclusion criteria included women with a history of breast cancer at baseline or missing breast cancer status at baseline (n=5,074), those who reported breast removal at baseline (n=272), women reporting any cancer at or prior to baseline, except for nonmelanoma skin cancer (n=6,313), any cancer (including breast cancer) diagnosed within three years from baseline during the follow-up period (n=3,609), breast cancer diagnosed as second primaries during follow-up (n=213), women with reported total energy intake values judged to be implausible (< 600 kcal/day or > 5000 kcal/day) (n=4,584) or extreme BMI values ($< 15\text{kg/m}^2$ or $> 50\text{kg/m}^2$) (n=564), as well as participants with single FFQs (n=20,901). Additionally, we excluded participants with missing data in the covariates included in the multivariable-adjusted models (n=10,442); leaving a total of 70,998 participants for the final analyses (80.2% in the OS and 19.8% in the DM control group). Frequencies and percentages were computed to describe the distribution of covariates across quintiles of average DII.

To determine the role of history of the inflammatory potential of diet on breast cancer risk, we calculated the average DII between baseline and Year 3 for the OS and between Year 1 and composite Year 3 for the DM control group [40]. The average DII scores were then categorized into quintiles and used in multiple Cox regression models to estimate hazard ratios (HR) for the incidence of invasive breast cancer and its molecular and histological subtypes. To determine the role of patterns of change in the inflammatory potential of diet over time in breast cancer risk, we calculated DII scores and categorized them into quintiles (Q) at both time points. We then further categorized the changes in the inflammatory potential of diet based on quintile differences between the first and second time points, as follows:

1. Anti-inflammatory stable: Q1 or Q2 at both time points or change from Q3 to Q2;
2. Anti-inflammatory change: changes -2Q ;
3. Neutral inflammation stable: changes from Q2 to Q3, Q4 to Q3 or stable at Q3 at both time points;
4. Pro-inflammatory change: changes 2Q ;

5. Pro-inflammatory stable: Q4 or Q5 at both time points, or change from Q3 to Q4.

The names of these patterns of change in DII were meant to be qualitative. Next, Cox regression models were used to estimate hazard ratios and 95% CI for the incidence of invasive breast cancer including the molecular and histological subtypes, by patterns of change in DII, with adjustment for multiple covariates. The anti-inflammatory stable category, considered to be the healthiest category, was the reference for all models.

Potential confounding variables were selected based on previous literature or based on a change in univariate HRs by >10%. All multivariable-adjusted models included the following covariates as potential confounders: age (years, continuous), race/ethnicity (European American, African American, Hispanic, Asian or Pacific Islander and Other); educational level (less than high school, some high school /GED, at least some college/graduate education), smoking status (current, past, and never), body mass index (BMI) categories [BMI= weight(kg)/height(m)²] (normal or underweight (15 to <25kg/m²), overweight (25 to <30 kg/m²), and obese (≥ 30kg/m²)); physical activity (PA), categorized based on public health recommendations [41], as meeting or not meeting PA recommendations (≥ 150 minutes/week of moderate intensity PA or ≥ 75 minutes/week of vigorous intensity PA and <150 minutes/week of moderate intensity PA or <75 minutes/week of vigorous intensity PA, respectively); regular (at least twice a week for the previous 2 weeks) [42] use of non-steroidal anti-inflammatory drug (NSAID) (yes/no); duration of estrogen and progesterone use categorized into five groups (none, <5y, 5 to <10y, 10 to <15y, and ≥ 15y), family history of breast cancer (yes/no), mammography use within 2 years of baseline (yes/no), age at menarche (<10, 11–15, ≥ 16 years), number of live births (none, 1–3, ≥ 4), oophorectomy status (no ovaries removed, one or both ovaries removed), Hormone Therapy trial arm (estrogen-alone intervention, estrogen-alone control, estrogen & progesterone intervention, estrogen & progesterone control, not randomized to this trial), Calcium and Vitamin D trial arm (intervention, control, not randomized to this trial), and total energy intake (kcal/day). Data on potential confounding variables were collected by self-administered questionnaires, which ascertained demographics, medical history, and lifestyle factors [27].

Each covariate in the final models of both the average DII score and patterns of change in DII scores was tested for adherence to proportional hazards using cumulative sums of Martingale-based residuals [43], and none was found to be in violation. To determine whether the association between both the average DII score and patterns of change in DII scores and breast cancer incidence differed by race/ethnicity, education, smoking status, BMI, physical activity and NSAIDs use, we included interaction terms between each of these covariates and average DII score and assessed significant effect modification at *P* <0.10. None of the interaction terms was significant. Tests of linear trend between breast cancer incidence and increments of average DII score adjusted for multiple covariates were computed by assigning the median value of each quintile to each participant in the quintile, and this variable was entered into models as ordinal values. We evaluated 95% CIs to determine statistical significance. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC), and all tests were two-sided.

RESULTS

The average DII was 1.04 (standard deviation (SD): 1.85), ranging from a minimum of -5.79 to a maximum of +5.17. Table 1 shows the distribution of participants' characteristics across quintiles of the average DII scores. Participants with higher average DII scores (representing a more pro-inflammatory diet) consisted of a higher proportion of women who were African American or Hispanic, overweight or obese, current smokers, not meeting physical activity guidelines, reported not doing a mammogram within 2 years of baseline, and with lower educational attainment. In contrast, participants with a more anti-inflammatory diet consisted of a higher proportion of women who were European American or Asian/Pacific Islander, had a BMI in the range 15 to <25 kg/m², were highly educated, and adhered to PA guidelines. Participants were followed for a median of 16.05 years, accumulating a total of 1,093,947 person-years, during which 3,471 cases of invasive breast cancer were identified.

Table 2 presents HRs of the association between the average DII and risk of invasive breast cancer and subtypes. Overall, there was no significant association between average DII score and risk of invasive breast cancer (HR_{Q5vsQ1}, 1.03; 95%CI, 0.90, 1.17; $p_{\text{trend}}=0.79$) in the multivariable-adjusted model. In the analyses by cancer phenotype, we found a significant nonlinear association between average DII and risk of ER-, PR-, HER2+ subtype. Comparing extreme quintiles of average DII, women with a history of highly pro-inflammatory diets had a 137% higher risk of developing this subtype of breast cancer (HR, 2.37; 95%CI, 1.08, 5.20; $p_{\text{trend}}=0.18$, $n=99$ cases) compared to women with anti-inflammatory diets. Women presenting with the triple negative phenotype also showed higher risk from consuming pro-inflammatory diets but this was not statistically significant (HR, 1.41; 95%CI, 0.90, 2.21; $p_{\text{trend}}=0.31$, $n=282$ cases).

In the first 3 years of follow-up, 26.6% of participants were classified as having an anti-inflammatory stable dietary pattern, 11.4% had anti-inflammatory dietary changes, 24.4% were in the neutral inflammation stable category, 10.4% experienced pro-inflammatory changes, while 27.2% were in the pro-inflammatory stable category. Table 3 shows HRs for the association between patterns of change in DII scores and risk of invasive breast cancer for all participants and separately by breast cancer subtypes. Overall, no substantial association was found between patterns of change in DII scores over time and total invasive breast cancer (HR_{pro-inflammatory change vs. anti-inflammatory stable}, 1.06; 95%CI, 0.95, 1.18). However, participants in the pro-inflammatory stable category were at higher risk of ER-, PR-, HER2+ subtype breast cancer, compared to participants in the anti-inflammatory stable category in the age-adjusted model (HR, 1.82; 95%CI, 1.06, 3.13), and after adjusting for multiple potential confounding variables, the association persisted but was less precise and marginally significant (HR, 1.85; 95%CI, 0.96, 3.55), with a P -value of 0.06 associated with the HR.

DISCUSSION

In this large prospective study of the role of changes over time in, and history of the inflammatory potential of diet in breast cancer risk, we observed no substantial association

between either 1) the history of dietary inflammatory potential, or 2) change in dietary inflammatory potential over time, and risk of overall invasive breast cancer. However, changes towards pro-inflammatory diets and maintaining a highly pro-inflammatory diet over time was associated with higher risk of developing the ER–, PR–, HER2+ subtype of breast cancer in postmenopausal women. To the best of our knowledge, this is the first study to characterize the association between a history of, or changes over time in the inflammatory potential of diet, and risk of breast cancer.

Our results are generally similar to many previous prospective studies that have not observed significant associations between dietary patterns and overall invasive breast cancer risk [13, 14, 44], though these other studies assessed diet quality at only one point in time. Other previous studies have described heterogeneity of the association between dietary patterns and breast cancer by hormone receptor status [44–46]. Cottet *et al.*, found evidence of a higher risk of ER+/PR+ tumors with a Western dietary pattern and lower (i.e., inverse) risk of ER+/PR– tumors with a Mediterranean pattern in a French Cohort study [45]. In addition, the WHI DM trial investigated the effects of a low-fat dietary pattern on breast cancer risk by tumor characteristics including hormone receptor status and found evidence for a reduction in the occurrence of tumors that were ER+, PR– (P for difference=0.04). HER2 status was not available for breast cancers diagnosed early in that trial and was therefore not investigated [10]. Studies focusing on specific food groups such as fruits and vegetables have also reported differential findings by tumor subtype. For example, Fung *et al.*, found that higher consumption of fruits and vegetables was significantly associated with an inverse risk of ER– breast cancer in the Nurses' Health Study [44], while Gaudet *et al.*, found an inverse association between high fruit and vegetable intake and breast cancer risk among postmenopausal women with ER+ tumors [46]. In a pooled analysis which included data from 20 prospective cohort studies, Jung *et al.* observed no association between total fruit and vegetable intake and risk of overall breast cancer. However, vegetable consumption was inversely associated with risk of ER– tumors [47].

Overall, findings from these previous studies provide support for a potential differential role of diet on breast cancer risk by cancer phenotype, even though there is yet no consistency between specific breast cancer phenotypes and specific dietary patterns. Similar to our differential findings by HER2 subtypes, an Italian prospective study found an association between higher consumption of salad vegetables and lower risk of HER2+ breast cancer, and a suggestion of higher risk of HER2– breast cancer with more prudent dietary patterns [48]. It is not clear why a diet with higher inflammatory potential would be associated with a higher risk of ER–, PR–, HER2+ subtype of breast cancer, but some studies suggest that HER2+ breast tumors are associated with an increased amount of COX-2 protein which is involved in many inflammatory pathways [49]. COX-2 inhibitors also have been shown to suppress mammary tumor development in mice induced with HER2+ tumors [50]. There was no linear trend in the average DII, and risk was also higher in quintile 2, though not statistically significant, which suggests that the association is probably nonlinear.

Two previous studies have calculated the DII at one time point and examined its association with breast cancer risk, with conflicting results. Findings from a case-control study in postmenopausal German women are similar to the current study finding of no association

between DII scores and overall invasive breast cancer[25]. In a Swedish prospective study that included both pre- and postmenopausal women, there was a 22% higher risk of developing total breast cancer in postmenopausal women (HR, 1.22; 95%CI, 1.02, 1.46; $P_{\text{trend}}=0.03$), comparing extreme quartiles [24]. However, this study included both *in situ* and invasive breast cancer cases. Also, the dietary inflammatory potential of the Swedish study population was higher than in the current study; mean DII 2.67 versus 1.04.

Strengths of the current study include accounting for changes in the inflammatory potential of diet over time in a large, well-characterized population of almost 71,000 women, a long follow-up period, the inclusion of women of diverse race/ethnic groups, and the central adjudication of breast cancer diagnosis that included different subtypes. Our two main exposures, the average DII scores and change in the DII scores over time, were defined using two different approaches. The similarity in the results from these two exposures suggests that our findings are less likely to be accounted for by chance. There also is the problem of potential residual or unmeasured confounding, but we adjusted for many potential confounding variables. Measurement error is a limitation in most diet studies. We used an FFQ designed for use in this study population and averaged the DII at two different time points which could reduce within-person variability in diet. It also is important to note that components missing from the FFQ, including ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins, are anti-inflammatory. Even though we showed previously that reasonable predictive ability was retained when replacing 24-hour recall-derived DII scores with those from a structured questionnaire, there still may be lower predictive ability in this study population [35].

In conclusion, a history of pro-inflammatory diets or sustained intake of highly pro-inflammatory diets may be non-linearly associated with higher risk of developing ER-, PR-, HER2+ subtype of breast cancer. Our findings imply that dietary inflammatory potential may influence breast cancer risk differently by cancer phenotype and support the idea that breast cancer may not be one disease entity but a heterogeneity of diseases with potentially different risk factors. Studies with higher number of cancer cases for each phenotype are warranted to confirm the association between diet quality and different phenotypes of breast cancer.

Acknowledgments

Dr. Tabung and Dr. Hebert were supported by National Cancer Institute grants numbers F31 CA177255 and K05 CA136975, respectively. The WHI program was funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

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Table 1

Participants' characteristics across quintiles of average dietary inflammatory index^a (baseline^b to Year 3)

Characteristic	Q1 (-5.793 < -0.596) (more anti-inflammatory diet)	Q2 (-0.596, < 0.692)	Q3 (0.692, < 1.715)	Q4 (1.715, < 2.742)	Q5 (2.742, 5.167) (more pro-inflammatory diet)
Age (years), mean ± SD	63.4 ± 7.1	63.4 ± 7.1	63.2 ± 7.2	63.0 ± 7.2	62.8 ± 7.2
Race/ethnicity					
Asian or Pacific Islander	576 (4.1)	466 (3.3)	440 (3.1)	303 (2.1)	195 (1.4)
African American	567 (4.0)	703 (4.9)	752 (5.3)	966 (6.8)	1455 (10.2)
Hispanic/Latino	215 (1.5)	344 (2.4)	367 (2.6)	461 (3.3)	656 (4.7)
European American	12614 (89.0)	12569 (88.0)	12531 (87.7)	12281 (86.5)	11553 (82.1)
Other	197 (1.4)	193 (1.4)	187 (1.3)	188 (1.3)	215 (1.6)
Educational level					
Some high school or lower educational level	249 (1.8)	363 (2.5)	489 (3.5)	589 (4.1)	881 (6.2)
High school graduate/some college or associate degree	5877 (41.4)	6905 (48.4)	7601 (53.2)	8221 (57.9)	8980 (63.8)
4 years of college	8043 (56.8)	7008 (49.1)	6187 (43.3)	5389 (38.0)	4216 (30.0)
Smoking status					
Never	7388 (52.1)	7308 (51.2)	7189(50.3)	7214(50.8)	7293 (51.8)
Former	6308 (44.6)	6371 (44.3)	6317 (44.2)	6061 (42.7)	5585 (39.7)
Current	473 (3.3)	771 (5.5)	771 (5.5)	924 (6.5)	1199 (8.5)
Body mass index (kg/m²)					
Normal or underweight (15 to <25)	5886 (41.5)	5353 (37.5)	5151 (36.1)	4963 (35.0)	4840 (34.4)
Overweight (25.0 to <30)	4802 (33.9)	5004 (35.0)	5159 (36.1)	5053 (35.5)	4888 (34.7)
Obese (≥ 30)	3481 (24.6)	3919 (27.5)	3967 (27.8)	4183 (29.5)	4349 (30.9)
Physical activity (PA), minutes/week					
Not meeting PA recommendations	4181 (29.5)	5285 (37.0)	6054 (42.4)	6681 (47.0)	7639 (54.3)
Meeting PA recommendations	9988 (70.5)	8991 (63.0)	8223 (57.6)	7518 (53.0)	6438 (45.7)
NSAIDs use					
No	6105 (43.1)	6090 (43.7)	6005 (42.1)	5934 (41.8)	6068 (43.1)
Yes	8064 (56.9)	8186 (57.3)	8272 (57.9)	8265 (58.2)	8009 (56.9)

Characteristic	Q1 (−5.793 < −0.596) (more anti-inflammatory diet)	Q2 (−0.596, < 0.692)	Q3 (0.692, < 1.715)	Q4 (1.715, < 2.742)	Q5 (2.742, 5.167) (more pro-inflammatory diet)
Duration of estrogen and progesterone use					
None	9370 (66.1)	9683 (67.8)	9636 (67.5)	9801 (69.0)	9960 (70.7)
<5 Years	2293 (16.1)	2193 (15.3)	2173 (15.2)	2188 (15.4)	2022 (14.4)
5 to <10 Years	1344 (9.5)	1284 (9.0)	1349 (9.5)	1203 (8.5)	1148 (8.2)
10 to <15 Years	832 (5.9)	736 (5.2)	763 (5.3)	698 (4.9)	633 (4.5)
15+ Years	330 (2.3)	380 (2.7)	356 (2.5)	309 (2.2)	314 (2.2)
Mammography within 2 years of baseline					
Yes	12681 (89.5)	12719 (89.1)	12625 (83.4)	12442 (87.6)	12083 (85.8)
No	1488 (10.5)	1557 (10.9)	1652 (11.6)	1757 (12.4)	1994 (14.2)

^a Dietary inflammatory index components available in the WHI FFQ were: alcohol, beta-carotene, caffeine, carbohydrates, cholesterol, total energy, total fat, saturated fat, fiber, folic acid, iron, magnesium, niacin, riboflavin, thiamine, zinc, monounsaturated fatty acid(fa) polyunsaturated fatty acid, omega 3 fatty acid, omega 6 fatty acid, trans fat, protein, selenium, vitamins B12, B6, A, C, D, E, onion, green/black tea, isoflavones; while the following components were not available in the WHI FFQ: ginger, turmeric, garlic, oregano, rosemary, pepper, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins.

^b baseline to year 3 for Observational Study participants and year 1 to composite year 3 for Dietary Modification trial control group participants

Table 2

Risk of invasive breast cancer by subtype across quintiles of average dietary inflammatory index; Women's Health Initiative, 1993–2014

	Quintile 1 (more anti-inflammatory diet)		Quintile 2	Quintile 3	Quintile 4	Quintile 5 (more pro-inflammatory diet)	P _{trend} ^b
	Reference	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	
Invasive breast cancer							
Invasive breast cancer cases/non-cases	748/13421	717/13559	700/13577	631/13568	675/13402		
Age adjusted model	1.00	0.96 (0.86, 1.02)	0.94 (0.84, 1.04)	0.86 (0.77, 0.95)	0.94 (0.84, 1.04)		0.04
Multivariable adjusted model ^a	1.00	0.98 (0.88, 1.08)	0.97 (0.87, 1.07)	0.90 (0.80, 1.02)	1.03 (0.90, 1.17)		0.79
Molecular subtypes							
Triple negative (ER-, PR-, HER2-)							
Breast cancer cases/non-cases	53/13421	69/13559	42/13577	56/13568	62/13402		
Age adjusted model	1.00	1.30 (0.91, 1.86)	0.80 (0.53, 1.19)	1.07 (0.73, 1.56)	1.21 (0.84, 1.75)		0.67
Multivariable adjusted model	1.00	1.37 (0.95, 1.98)	0.87 (0.57, 1.34)	1.20 (0.79, 1.82)	1.40 (0.90, 2.19)		0.33
ER-, PR-, HER2+ subtype							
Breast cancer cases/non-cases	13/13421	25/13559	19/13577	13/13568	29/13402		
Age adjusted model	1.00	1.92 (0.98, 3.74)	1.46 (0.72, 2.95)	1.00 (0.46, 2.15)	2.26 (1.18, 4.35)		0.12
Multivariable adjusted model	1.00	1.95 (0.98, 3.86)	1.52 (0.73, 3.20)	1.05 (0.45, 2.41)	2.37 (1.08, 5.20)		0.18
Luminal A (ER+ and/or PR+, HER2-)							
Breast cancer cases/non-cases	499/13421	459/13559	475/13577	406/13568	422/13402		
Age adjusted model	1.00	0.92 (0.81, 1.04)	0.96 (0.85, 1.09)	0.83 (0.73, 0.94)	0.88 (0.77, 1.00)		0.01
Multivariable adjusted model	1.00	0.92 (0.81, 1.05)	0.96 (0.84, 1.10)	0.84 (0.73, 0.97)	0.92 (0.79, 1.09)		0.16
Luminal B (ER+ and/or PR+, HER2+)							
Breast cancer cases/non-cases	63/13421	55/13559	47/13577	46/13568	50/13402		
Age adjusted model	1.00	0.87 (0.61, 1.25)	0.75 (0.51, 1.09)	0.73 (0.50, 1.07)	0.81 (0.56, 1.18)		0.14
Multivariable adjusted model	1.00	0.93 (0.64, 1.35)	0.83 (0.55, 1.24)	0.86 (0.56, 1.32)	1.06 (0.67, 1.67)		0.91
Histologic subtypes							
Ductal carcinoma							
Breast cancer cases/non-cases	460/13410	434/13554	410/13569	400/13560	424/13391		

	Quintile 1 (more anti-inflammatory diet)				Quintile 5 (more pro-inflammatory diet)				P _{trend} ^b
	Reference	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	
Age adjusted model	1.00	0.95 (0.84, 1.09)	0.90 (0.79, 1.03)	0.88 (0.77, 1.01)	0.95 (0.83, 1.09)				0.21
Multivariable adjusted model	1.00	0.97 (0.85, 1.11)	0.93 (0.80, 1.07)	0.92 (0.79, 1.07)	1.03 (0.87, 1.21)				0.91
Lobular carcinoma									
Breast cancer cases/non-cases	66/13421	73/13559	74/13577	66/13568	68/13402				
Age adjusted model	1.00	1.10 (0.79, 1.54)	1.13 (0.81, 1.57)	1.02 (0.72, 1.43)	1.07 (0.77, 1.51)				0.83
Multivariable adjusted model	1.00	1.15 (0.82, 1.61)	1.19 (0.84, 1.69)	1.11 (0.76, 1.62)	1.25 (0.83, 1.88)				0.37

^aAll multivariable models were adjusted for age, race/ethnicity, educational level, smoking status, body mass index, physical activity, regular NSAID use, duration of estrogen and progesterone use, family history of breast cancer, mammography use within 2 years of baseline, age at menarche, number of live births, oophorectomy status, hormone therapy trial arm, CaD arm and total energy intake.

^bThe p value for trend was obtained by assigning median average DII values to each participant in the quintile and entering this ordinal variable in the models.

Table 3

Risk of breast cancer by subtype, across patterns of change in the dietary inflammatory index over a 3-year period of time; Women's Health Initiative, 1993–2014

	Patterns of DII quintile changes					
	Anti-inflammatory stable		Anti-inflammatory change		Pro-inflammatory stable	
	Referent	HR (95%CI) ^a	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Invasive breast cancer						
Invasive breast cancer cases/non-cases	987/17889	374/7726	823/16488	349/7063	938/18361	
Age adjusted model	1.00	0.90 (0.80, 1.01)	0.92 (0.84, 1.01)	0.93 (0.82, 1.05)	0.96 (0.87, 1.05)	
Multivariable adjusted model ^a	1.00	0.93 (0.83, 1.05)	0.95 (0.87, 1.05)	1.01 (0.88, 1.15)	1.06 (0.95, 1.18)	
Molecular subtypes						
Triple negative (ER–, PR–, HER2–)						
Breast cancer cases/non-cases	71/17889	39/7726	58/16488	29/7063	85/18361	
Age adjusted model	1.00	1.30 (0.88, 1.91)	0.90 (0.63, 1.27)	1.06 (0.69, 1.64)	1.20 (0.88, 1.65)	
Multivariable adjusted model	1.00	1.33 (0.89, 1.97)	0.98 (0.68, 1.40)	1.23 (0.77, 1.97)	1.39 (0.95, 2.04)	
ER–, PR–, HER2+ subtype						
Breast cancer cases/non-cases	20/17889	15/7726	19/16488	8/7063	37/18361	
Age adjusted model	1.00	1.75 (0.90, 3.42)	1.03 (0.55, 1.94)	1.03 (0.46, 2.35)	1.82 (1.06, 3.13)	
Multivariable adjusted model	1.00	1.80 (0.91, 3.55)	1.07 (0.56, 2.05)	1.01 (0.42, 2.42)	1.85 (0.96, 3.55)	
Luminal A (ER+ and/or PR+, HER2–)						
Breast cancer cases/non-cases	657/17889	235/7726	541/16488	241/7063	587/18361	
Age adjusted model	1.00	0.85 (0.73, 0.98)	0.91 (0.82, 1.02)	0.96 (0.83, 1.12)	0.90 (0.81, 1.01)	
Multivariable adjusted model	1.00	0.88 (0.75, 1.02)	0.92 (0.82, 1.04)	1.02 (0.87, 1.20)	0.97 (0.85, 1.11)	
Luminal B (ER+ and/or PR+, HER2+)						
Breast cancer cases/non-cases	80/17889	22/7726	65/16488	22/7063	72/18361	
Age adjusted model	1.00	0.65 (0.40, 1.03)	0.89 (0.64, 1.23)	0.71 (0.44, 1.14)	0.89 (0.65, 1.23)	
Multivariable adjusted model	1.00	0.70 (0.43, 1.12)	1.00 (0.71, 1.41)	0.89 (0.54, 1.48)	1.18 (0.80, 1.74)	
Histologic subtypes						

Patterns of DII quintile changes					
Anti-inflammatory stable		Anti-inflammatory change	Neutral inflammation stable	Pro-inflammatory change	Pro-inflammatory stable
	Referent	HR (95%CI) ^a	HR (95%CI)	HR (95%CI)	HR (95%CI)
Ductal carcinoma					
Breast cancer cases/non-cases	610/17876	227/7723	488/16479	215/7059	588/18347
Age adjusted model	1.00	0.88 (0.76, 1.03)	0.88 (0.78, 0.99)	0.92 (0.79, 1.08)	0.96 (0.86, 1.08)
Multivariable adjusted model	1.00	0.91 (0.78, 1.06)	0.91 (0.80, 1.03)	0.99 (0.84, 1.17)	1.05 (0.91, 1.20)
Lobular carcinoma					
Breast cancer cases/non-cases	88/17889	43/7726	86/16488	37/7063	93/18361
Age adjusted model	1.00	1.16 (0.80, 1.66)	1.08 (0.80, 1.45)	1.10 (0.75, 1.62)	1.07 (0.80, 1.43)
Multivariable adjusted model	1.00	1.25 (0.86, 1.81)	1.13 (0.82, 1.54)	1.21 (0.80, 1.84)	1.21 (0.86, 1.71)

^aAll multivariable models were adjusted for age, race/ethnicity, educational level, smoking status, body mass index, physical activity, regular NSAID use, duration of estrogen and progesterone use, family history of breast cancer, mammography use within 2 years of baseline, age at menarche, number of live births, oophorectomy status, hormone therapy trial arm, CaD arm and total energy intake.