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Original article

# Dietary inflammatory index and incidence of breast cancer in the SUN project

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SUMMARY

*Background & aims:* Breast cancer (BC) is the most commonly diagnosed cancer, and diet is suspected to play a role in its development. Dietary factors may mediate this process through modulation of inflammation, though findings from previous studies have not been consistent. We aimed to longitudinally assess the association between the dietary inflammatory index (DII®), a frequently used method to assess the inflammatory potential of the diet, and incident BC.

*Methods:* We included 10,713 middle-aged, Spanish female university graduates from the SUN cohort. DII® scores were derived from a validated 136-item food-frequency questionnaire, and it was based on scientific evidence on the relationship between diet and inflammatory biomarkers. Diagnosis of BC was reported by the participant or, if deceased, by the next of kin or identified from death certificates. Self-reports of BC were confirmed by revision of medical reports by an experienced oncologist. Cox proportional hazard models were used to estimate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association between quartiles of DII® and incident BC.

*Results:* After 10.3 years of median follow-up, we identified 100 confirmed and 168 probable incident BC cases. The multivariable-adjusted HR for participants in the 4th quartile to the 1st quartile was 1.44 (95% CI 0.76–2.72; p-trend: 0.339) when confirmed cases were analyzed, and 1.20 (95% CI 0.72–1.99; p-trend: 0.757) for the probable cases. We neither observed statistically significant differences in regard to menopausal status.

*Conclusions:* The apparent increase in risk between DII® scores and BC in our cohort was not statistically significant, which could be partly explained by the small number of observed cases.



## 1. Introduction

Breast cancer (BC) is the most frequently diagnosed malignant tumor, and it is the most common malignancy among women [1,2]. In 2015, 2.4 million new BC diagnoses were made worldwide. BC is the fifth most frequent cause of death among different tumor types (533,000 deaths in the world), the third cause of death among women in developing countries, and the fourth in the most developed areas [3]. Not only because of current burden of disease

*Abbreviations:* BC, Breast Cancer; DII®, Dietary inflammatory index; SUN, Seguimiento Universidad de Navarra. Follow-up University of Navarra; HR, hazard ratio; RR, Relative Risk; OR, Odds Ratio; SD, standard deviation; CI, confidence interval; BMI, body mass index; MET, metabolic equivalent index; CRP, C-reactive protein; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; WHI, Women's Health Initiative.

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but also because of dismal predicted trends for this illness, preventive strategies that may help to address this concern becomes a public health priority.

Non-modifiable as well as modifiable risk factors have been described for BC [4–7]. Among the latter, the only accepted associations with BC incidence are oral contraceptives [8], menopausal hormone replacement therapy [9], late parity, alcohol consumption [10–12], not breastfeeding [13], excess body fat [14] and lack of physical exercise [15–18]. Regarding dietary factors, the results of the different investigations are inconsistent [19–22].

Despite inconsistencies, a high-quality dietary pattern has been suggested to reduce the risk of BC [6, 19]. A healthy diet, such as the Mediterranean dietary pattern [20, 22, 23, 24] and other dietary patterns rich in vegetables, fruits and fish [21,25], have been suggested to exert their beneficial effect in cancer prevention through different mechanisms involved in the initiation, promotion and progression of cancer. Some of the reported mechanisms are: antioxidant effect (due to high quantity of polyphenols in these foods) [26, 27], inhibiting growth and metastatic potential of cancer cells [28, 29], inhibition of autophagy [30], transcriptional repression of human epidermal growth factor receptor 2 (HER2) [31], inhibiting cell proliferation and invasiveness [32], aromatase inhibition [33] and reduction of endogenous estrogen production [34]. One of the most studied mechanisms is the potential of diet in changing the inflammatory status [35–38]. In fact, a large body of evidence has shown an association between diet and regulation of low-grade inflammatory status (as appraised by elevated levels of highly-sensitive C-reactive protein and other pro-inflammatory cytokines) [39–43]. These cytokines also have been linked to BC appearance, as well as with disease progression, through mechanisms related to stimulation of angiogenesis, proliferation, migration and metastasis and apoptosis prevention [44–47]. On the other hand, inflammation, especially chronic inflammation [48], have been suggested to be involved in the development of BC (and other cancers), through immunosuppression [49] or up-regulation of oncoproteins [50]. In this context of the possible role of inflammation in the development of BC, it is interesting to consider that many beneficial effects of the Mediterranean diet have been attributed to the anti-inflammatory properties of the typical foods of the Mediterranean diet. The dietary inflammatory index (DII®) was specifically developed to capture the inflammatory potential of diet, and it provides quantitative information about this inflammatory potential of the diet [39]. It has been used in different populations with inconsistent results, especially with respect to BC [51–60]. No prospective study has been conducted thus far on the association between DII scores and BC in a Mediterranean country. Thus, our aim is to study this possible association between DII scores and BC incidence among Spanish women in the SUN Project.

## 2. Material and methods

### 2.1. Study population

This work is framed in the "Seguimiento Universidad de Navarra" Project (University of Navarra follow-up Project). The SUN Project is an ongoing, multipurpose, prospective and dynamic cohort, in which more than 22,000 Spanish university graduates have been included and followed up for a median of 9.5 years to assess associations between diet and lifestyles and the incidence of several chronic diseases and mortality. The study design, methods and cohort profile have been published in detail elsewhere [61]. Briefly, beginning in December 1999, highly educated participants, all of them university graduates, are contacted biennially. Enrollment is permanently open, and follow-up is conducted through biennial mailed questionnaires about lifestyle factors and medical conditions.

Through December 1, 2016, 22,564 participants had been recruited and had completed the baseline questionnaire of the SUN Project. We analyzed data of the women included in the cohort by that time (n = 13,843). To include those women who have had the chance to answer at least one of the biennial follow-up questionnaires, we included in the present analysis those women recruited before March 1, 2014 (n = 13,645).

Out of these women, we excluded those from whom we had no information during follow up (n = 1286, retention rate 91%), women with prevalent BC or any other previous cancer (n = 102), women with a daily energy intake out of the pre-defined limits (below 500 or beyond 3500 kcal/day) (n = 1345), and women with reported menopause before 35 years of age (n = 199). Thus, the effective sample size was 10,713 women (Fig. 1).

All potential participants were duly informed of their right to refuse to participate in the SUN study or to withdraw their consent to participate at any time without reprisal, according to the principles of the Declaration of Helsinki. Special attention was given to the specific information needs of individual potential candidates as well as to the methods used to deliver their information and the feedback that may receive in the future from the research team. After ensuring that the candidate had understood the information, we sought their potential freely given informed consent, and their voluntary completion of the baseline questionnaire. These methods were accepted by our Institutional Review Board as to imply an appropriately-obtained informed consent.

### 2.2. Dietary assessment

We used a 136-item semi-quantitative food-frequency questionnaire (FFQ) previously validated in Spain to assess baseline

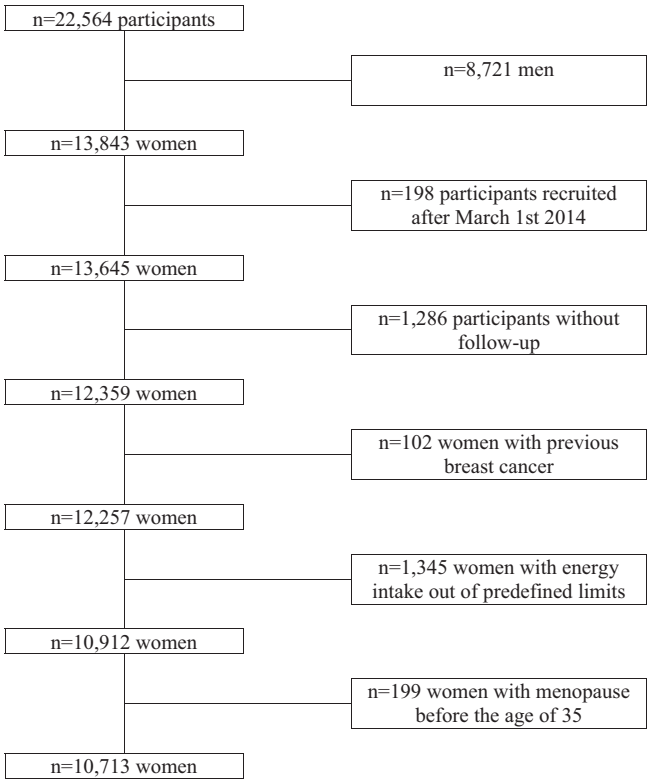


**Fig. 1.** Flow-chart of participants recruited in the SUN Project, 1999–2016.

dietary habits [62]. We analyzed the regularity of consumption of standardized portion sizes for all food items to estimate the nutrient scores. A trained dietician updated the nutrient information with updated food composition tables for Spain [63,64].

### 2.3. The dietary inflammatory index (DII®)

The development of the DII® has been described elsewhere [39]. Briefly, the DII® is a population-based score calculated from an extensive review of the literature published from 1950 to 2010, including 1943 articles to a total of 45 food parameters comprising various macronutrients, micronutrients, flavonoids and individual food items. It was developed to describe the inflammatory characteristics of diet, considering the effect of each parameter in six inflammatory biomarkers (IL-1b, IL-4, IL-6, IL-10, TNF-$\alpha$ and C-reactive protein). In this regard, the greater the DII score, the more pro-inflammatory the diet. More negative values represent more anti-inflammatory diets.

Based on the review of the literature, each parameter was given a score based on its inflammatory potential according to its association with previously mentioned inflammatory biomarkers: +1 if they were positively associated, −1 if they were negatively associated, or 0 if they were not associated. A z-score was calculated for each food consumed by deducting the "standard global mean" from the reported amount and dividing this value over the standard deviation. This value was then transformed to a proportion to dampen the effect of "right skewing". To create a distribution approximately symmetrical around zero, each proportion was double and then 1 was subtracted. These food parameter-specific DII scores were then summed to obtain the overall DII score for each participant.

Construct validation of the DII® was performed using data from the SEASONS study, which contained information on dietary intake from two sources (multiple days of 24-h recalls and a 7-day dietary recall) [65] and serum high-sensitivity C-reactive protein (CRP) as the construct validator [39]. So far, the DII® has been linked to inflammatory cytokines including CPR and IL-6 [66], obesity [67], and several inflammation-related diseases [68–71].

In this study, a total of 28 food parameters considered in the DII® score were derived from the FFQ and therefore were used to calculate the DII score. These include total energy intake and the intake of carbohydrate, protein, total fat, alcohol, fiber, cholesterol, saturated fat, mono-unsaturated fat, omega-3 fatty acids, omega-6 fatty acids, trans-fatty acids, niacin, thiamin, riboflavin, vitamin B12, vitamin B6, iron, magnesium, selenium, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid and caffeine.

### 2.4. Evaluation of covariates

Information about lifestyles, medical history, anthropometric measures, reproductive history, and sociodemographic factors was collected in the baseline questionnaire. Physical activity was assessed with a previously validated questionnaire [72]. We estimated metabolic equivalents (METs) for each participant to yield METs-h/week scores. Previously, accuracy of self-reported weight and height for body mass index (BMI) calculation was authenticated in a subsample of this cohort [73].

### 2.5. Ascertainment of incident breast cancer cases

The primary end point for the present analysis was the diagnosis of new cases of BC. Women self-reported to have received a new diagnosis cases of BC in the biennial follow-up questionnaires. Fatal cases were reported to our research team by the subjects' next of kin, postal authorities or work associates. For participants lost to follow-up or with unknown causes of death, the National Death Index was consulted to identify deceased cohort members, and to obtain the cause of death. Participants (or their proxies) who reported any of these diagnoses on a follow-up questionnaire were asked for a copy of their medical records in order to confirm the information. A trained oncologist confirmed the cases. All confirmed cases, together with self-reported breast cancer diagnoses that could not be further confirmed, were considered for the analyses as probable incident cases.

### 2.6. Statistical analysis

We described baseline characteristics of our participants with means and standard deviation (SD) for continuous variables and percentages for categorical variables across quartiles of the DII scores. Significance testing for differences in quantitative traits across quartiles of the DII was conducted using analysis of variance (ANOVA). Chi-squared tests were used for qualitative traits.

We calculated person-years of follow-up for each participant from the date of completion of the baseline questionnaire to the date of BC diagnosis, the date of death, or the date of return of the last follow-up questionnaire, whichever occurred first. Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using Cox proportional hazard models considering the lowest quartile of DII® (most anti-inflammatory) as the reference category and with age as underlying time-variable. In an attempt to control for potential confounding factors, we used successive degrees of adjustment: 1) adjustment for age (underlying time variable and 3 strata) and stratification by calendar year of recruitment; 2) additional adjustment for height, years at university, number of relatives with history of BC (none, one or two relatives out of mother, sisters and/or grandmothers), smoking status (never smoker, former smoker, current smoker), physical activity (METs-h/week, continuous), alcohol intake (g/d, continuous), BMI (<25 kg/m$^2$, 25 to <30 kg/m$^2$, and ≥30 kg/m$^2$), age at menarche (<10 years old, 10 to <12 years, 12 to <14 years, 14 to <16 years, and ≥16 years), age at menopause (<50 years old, from 50 to 54.9, and ≥55 years), number of pregnancies of more than 6 months (continuous), pregnancy before the age of 30 years (dichotomous), months of breastfeeding (continuous), use of hormone replacement therapy (dichotomous) and its duration (continuous); and 3) additional adjustment for diabetes (dichotomous) and total energy intake (kcal/d, continuous). For analyses on postmenopausal BC, we additionally adjusted for the years since recruitment until the beginning of the time at risk.

We conducted tests of linear trend assigning to each quartile of DII score its quartile-specific median and using the resulting variable as continuous in the abovementioned models. Confounder selection was decided *a priori* based on the literature.

In a second step, we assessed the differences in the observed association between the DII and pre- or postmenopausal BC. Information on age at menopause was collected in the baseline questionnaire and after 16 years of follow-up. For women lacking information on their age at menopause (n = 9309) we imputed their postmenopausal status according to the 75th percentile of age at menopause in the study population (52 years of age) [57]. For premenopausal BC as outcome, we excluded those women who reported having had menopause before study inception and censored follow-up time at the age of 52 years or at the age of menopause, whichever occurred first. For postmenopausal BC as outcome, we only considered as time at risk the time of follow-up after having turned 52 years old or having had their menopause, whichever occurred later.

Finally, we compared women with a pro-inflammatory diet (DII≥0) with women consuming an anti-inflammatory diet (DII<0) and estimated the Cox regression models for total, premenopausal

and postmenopausal BC with adjustment for the same potential aforementioned confounders.

Taking into account that the overall incidence of BC in the SUN Project was 1.5% and that we had 2678 women in each quartile, our sample size would allow us to detect differences of 1.1% in the incidence of BC between extreme quartiles with a statistical power of 80% and assuming a two-sided alpha error of 5%.

All p values were two-sided and a p value < 0.05 was deemed as statistically significant. All analyses were performed with Stata/SE 13.0.

## 3. Results

Table 1 shows the main characteristics of the study participants according to quartiles of the DII score. The median DII score was −1.51, ranging from a maximum anti-inflammatory value of −5.67 to a maximum pro-inflammatory value of +6.11. Two thousand participants had a DII score ≥0 (i.e., pro-inflammatory) and 8709 had a DII score < 0 (i.e., anti-inflammatory). The mean (SD) age of the participants at recruitment was 35 years [11]. Women in the highest DII (most pro-inflammatory) quartile were more likely to be former smokers, premenopausal, had fewer pregnancies of >6 months, were less likely to have been pregnant before the age of 30 years, and had breastfed for less time that women eating a more anti-inflammatory diet. Women in the lowest DII (most anti-inflammatory) quartile were more likely to be older, and more physically active, and consumed more total energy and alcohol.

### 3.1. DII scores and risk of BC

During a median follow-up time of 10.3 years and 105,847 person-years at risk, 168 probable incident cases of BC were registered. When only confirmed cases were considered, 100 cases among 106,189 person-years of follow-up were identified. The incidence rate was 9.3 per 10,000 person-years, ranging from 9.7 per 10,000 person-years in the most anti-inflammatory quartile of DII scores to 10.08, 6.72 and 10.83 in quartiles 2 to 4, respectively.

Table 2 presents the HRs for the association between DII® and probable cases of BC in three different models. We observed no significant associations in any of the three models. The HR for the association between DII and BC in the fully adjusted model for women in the 4th quartile of DII compared to women in the first quartile of DII® was 1.20 (95% CI 0.72–1.99; P for trend = 0.757). When we compared women with a pro-inflammatory diet vs. women with an anti-inflammatory diet, we found a HR = 1.23 (95% CI 0.79–1.91) in the fully adjusted model. In Table 3, we show the results for the association between the DII and only confirmed cases of BC. In the age-adjusted model, the HR for the comparison between

**Table 1**
Baseline characteristics of participants across quartiles of the dietary inflammatory index. The SUN Project, 1999–2014.

| Variable | Quartiles of DII score | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | P value |
| | More anti-inflammatory | | | More pro-inflammatory | |
| Median DII® | −3.39 | −2.31 | −1.26 | 0.66 | |
| Range of DII® | (−5.67,−2.8) | (−2.8,−1.85) | (−1.85,−0.52) | (−0.52,6.11) | |
| N | 2679 | 2678 | 2678 | 2678 | |
| Age (years) | 36.3 (11.3) | 34.9 (10.5) | 34.5 (10.4) | 33.4 (9.8) | <0.001 |
| Body mass index (kg/m$^2$) | 22.3 (3.1) | 22.2 (3) | 22.2 (3) | 22.1 (3.1) | 0.173 |
| Physical activity (METs-h/w) | 28.2 (23) | 25.1 (20) | 23.7 (19.6) | 20.2 (17.5) | <0.001 |
| Total energy intakel (kcal/d) | 2660 (492) | 2432 (494) | 2222 (484) | 1871 (507) | <0.001 |
| Alcohol intake (g/day) | 5.11 (7.34) | 3.96 (5.49) | 3.67 (5.4) | 3.34 (4.9) | <0.001 |
| Years at university | 4.83 (1.34) | 4.82 (1.34) | 4.82 (1.32) | 4.84 (1.32) | 0.972 |
| Height (cms) | 164 (6) | 164 (6) | 164 (6) | 163 (6) | 0.044 |
| Number of pregnancies of more than 6 months | 0.7 (1.14) | 0.73 (1.16) | 0.71 (1.16) | 0.59 (1.14) | <0.001 |
| Breast-feeding months | 2.50 (5.18) | 2.69 (5.25) | 2.33 (4.88) | 1.86 (4.77) | <0.001 |
| Time of hormone replacement therapy (years)[1] | 1.19 (2.26) | 1.40 (2.48) | 1.39 (2.54) | 1.24 (2.23) | 0.639 |
| Diabetes (%) | 1.42 | 1.16 | 1.19 | 0.67 | 0.065 |
| Pregnancie before age of 30 (%) | 19.4 | 21 | 19.5 | 17.1 | 0.003 |
| Tobacco (%) | | | | | |
| Never smoker | 50.8 | 52.2 | 48.9 | 47.4 | |
| Former smoker | 24.4 | 23.5 | 26.4 | 31.3 | |
| Current smoker | 22.1 | 21.9 | 22.1 | 18.5 | <0.001 |
| Number of relatives with BC (%)[2] | | | | | |
| 0 | 89.1 | 89.6 | 89.3 | 89.5 | |
| 1 | 8.92 | 8.22 | 9.08 | 8.4 | |
| 2 | 2.02 | 2.17 | 1.64 | 2.09 | 0.703 |
| Age of menarche (%) | | | | | |
| <10 years | 1.23 | 1.08 | 1.23 | 1.12 | |
| 10–11 years | 18.6 | 20.2 | 18.9 | 18.6 | |
| 12–13 years | 54.1 | 55.2 | 54.7 | 54.9 | |
| 14–16 years | 23.1 | 21.2 | 22.8 | 22.9 | |
| >16 years | 2.95 | 2.39 | 2.39 | 2.43 | 0.764 |
| Menopausal status (%) | | | | | |
| Premenopausal (%) | 83.6 | 87.6 | 88.5 | 90.7 | |
| Postmenopausal (%) | 13.83 | 10.25 | 9.88 | 7.49 | 0.001 |
| Postmenopausal <50 years (%) | 65.28 | 65.20 | 65.48 | 69.09 | |
| Postmenopausal 50–55 years (%) | 33.01 | 33.45 | 32.74 | 30.00 | |
| Postmenopausal ≥ 55 years (%) | 1.71 | 1.35 | 1.78 | 0.91 | 0.672 |

DII®: dietary inflammatory index, BC: breast cancer.
P values were obtained from ANOVA for quantitative traits and from chi-squared tests for qualitative traits.
(1) Only among postmenpausal women.
(2) Information from mother, sister, and both grandmothers was collected.

**Table 2**
Hazard ratio (IC 95%) including the probable breast cancer cases for each quartile of DII® in the SUN Project.

| Variable | Quartiles of DII scores | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | P for trend |
| | Most anti-inflammatory | | | Most pro-inflammatory | |
| Cases | 43 | 50 | 34 | 41 | |
| Person-years of follow up | 26,395 | 26,556 | 26,200 | 26,696 | |
| Incidence rate/10,000 person year | 16.29 | 18.83 | 13.00 | 15.36 | |
| Age adjusted HR[1] | 1 (ref) | 1.22 (0.82–1.84) | 0.86 (0.55–1.36) | 1.10 (0.71–1.69) | 0.993 |
| Model 1[2] | 1 (ref) | 1.22 (0.81–1.84) | 0.83 (0.53–1.31) | 1.05 (0.68–1.63) | 0.827 |
| Model 2[3] | 1 (ref) | 1.26 (0.83–1.92) | 0.89 (0.55–1.43) | 1.20 (0.72–1.99) | 0.757 |

DII®: dietary inflammatory index.
[1]: Adjustment for age.
[2]: Additional adjustment for height (continous), number of relatives with history of BC (3 categories), smoking status (never smoker, former smoker, current smoker), physical activity (METs-h/wk, continuous), alcohol intake (g/d, continuous), BMI (3 categories), age of menarche (5 categories), age of menopause (3 categories), number of pregnancies of more than 6 months (continuous), pregnancy before the age of 30 years (dichotomous), months of breastfeeding (continuous), use of hormone replacement therapy (dichotomous) and its duration (continuous), and years at university (continous).
[3]: Model 2 additional adjustment for diabetes (dichotomous) and total energy intake (kcal/d, continuous).

extreme quartiles (Q4 vs. Q1) was 1.33 (95% CI 0.78–2.28; P for trend = 0.387). In the fully adjusted model, the HR for the comparison of Q4 vs. Q1 was 1.44 (95% CI 0.76–2.72; P for trend = 0.339). In many of the models, we observed the highest increase of the risk of developing BC according to a more pro-inflammatory diet (Q4) compared to those participants in the most anti-inflammatory group (Q1), although no association reached statistical significance. Women with a pro-inflammatory diet showed a HR of overall BC of 1.41 (95% CI 0.77–2.59) compared with women with an anti-inflammatory diet in the fully adjusted model.

In Table 4 we present the results separately for premenopausal and postmenopausal BC for all the probable cases. In premenopausal women, the HR for BC in the fully adjusted model was 1.01 (95% CI 0.53–1.93; P for trend = 0.966); while for postmenopausal BC the HR was 1.57 (95% CI 0.64–3.83; P for trend = 0.566). The comparison for women with a pro-inflammatory diet vs. women with an anti-inflammatory diet was not statistically significant for premenopausal women [HR = 1.16 (95% CI 0.67–2.01)] nor for postmenopausal women [HR = 1.65 (95% CI 0.72–3.80)] in the fully adjusted model. When we considered only confirmed cases of BC (Table 5), we neither observed significant associations between DII and incident premenopausal BC (HR Q4 vs. Q1: 1.21 (95% CI 0.51–2.87; P for trend = 0.527)) or postmenopausal BC (HR Q4 vs. Q1 in the most adjusted model: 2.00 (95% CI 0.71–5.64); P for trend = 0.304)). A pro-inflammatory diet was not significantly associated to the risk of BC compared with an anti-inflammatory diet when we considered premenopausal [HR = 1.51 (95% CI 0.69–3.32)] or postmenopausal BC [HR = 1.25 (95% CI 0.37–4.24)] as outcome in the fully adjusted model.

## 4. Discussion

Based on the prospective SUN cohort, we observed no statistically significant association between a more pro-inflammatory diet (higher quartile of the DII score) and overall risk of BC. In ancillary analyses, according to menopausal status, we found similar evidence for both pre- and post-menopausal women. Nevertheless, all the point estimates of the HRs in the adjusted models for the fourth vs. the first quartile were greater than 1.

Available evidence about the relationship between the pro-inflammatory potential of diet and BC is inconsistent [51–53,55]. *Ge et al.* [51] conducted a study to evaluate the association between energy-adjusted DII and postmenopausal BC risk in a German population-based case-control study. In that study, 2887

**Table 3**
Hazard ratio (IC 95%) of confirmed breast cancer cases for each quartile of DII® in the SUN Project.

| Variable | Quartiles of DII score | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | P for trend |
| | Most anti-inflammatory | | | Most pro-inflammatory | |
| Cases | 26 | 27 | 18 | 29 | |
| Person-years of follow up | 26,473 | 26,673 | 26,270 | 26,772 | |
| Incidence rate/10,000 person year | 9.82 | 10.12 | 6.85 | 10.83 | |
| Age adjusted HR[1] | 1 (ref) | 1.11 (0.65–1.90) | 0.77 (0.42–1.41) | 1.33 (0.78–2.28) | 0.387 |
| Model 1[2] | 1 (ref) | 1.07 (0.62–1.85) | 0.73 (0.39–1.34) | 1.20 (0.70–2.07) | 0.623 |
| Model 2[3] | 1 (ref) | 1.13 (0.65–1.96) | 0.79 (0.42–1.49) | 1.44 (0.76–2.72) | 0.339 |

DII®: dietary inflammatory index.
[1]: Adjustment for age.
[2]: Additional adjustment for height (continous), number of relatives with history of BC (3 categories), smoking status (never smoker, former smoker, current smoker), physical activity (METs-h/wk, continuous), alcohol intake (g/d, continuous), BMI (3 categories), age of menarche (5 categories), age of menopause (3 categories), number of pregnancies of more than 6 months (continuous), pregnancy before the age of 30 years (dichotomous), months of breastfeeding (continuous), use of hormone replacement therapy (dichotomous) and its duration (continuous), and years at university (continuous).
[3]: Model 2 additional adjustment for diabetes (dichotomous) and total energy intake (kcal/d, continuous).

**Table 4**
Hazard ratio (IC 95%) including the probable breast cancer cases for each quartile of DII® in the SUN Project for pre- and post-menopausal women.

| Variable | Quartiles of DII scores | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | P for trend |
| | Most anti-inflammatory | | | Most pro-inflammatory | |
| Premenopausal breast cancer | | | | | |
| N | 2244 | 2355 | 2377 | 2440 | |
| Cases | 26 | 28 | 26 | 26 | |
| Person-years of follow up | 19972 | 21343 | 21308 | 22604 | |
| Incidence rate/10,000 person-year | 13.02 | 13.12 | 12.20 | 11.50 | |
| Age adjusted HR[1] | 1 (ref) | 1.05 (0.62–1.81) | 1.01 (0.58–1.74) | 0.99 (0.58–1.73) | 0.942 |
| Model 1[2] | 1 (ref) | 1.05 (0.61–1.81) | 0.97 (0.56–1.69) | 0.98 (0.56–1.71) | 0.873 |
| Model 2[3] | 1 (ref) | 1.06 (0.61–1.84) | 0.98 (0.55–1.75) | 1.01 (0.53–1.93) | 0.966 |
| Postmenopausal breast cancer | | | | | |
| N | 862 | 720 | 672 | 575 | |
| Cases | 16 | 14 | 6 | 13 | |
| Person-years of follow up | 5641 | 4321 | 4256 | 3372 | |
| Incidence rate/10,000 person year | 28.36 | 32.40 | 14.10 | 38.54 | |
| Age adjusted HR[1] | 1 (ref) | 1.09 (0.53–2.25) | 0.48 (0.19–1.23) | 1.30 (0.62–2.72) | 0.749 |
| Model 1a[2] | 1 (ref) | 1.07 (0.52–2.21) | 0.44 (0.17–1.15) | 1.22 (0.56–2.62) | 0.917 |
| Model 2a[3] | 1 (ref) | 1.17 (0.56–2.47) | 0.51 (0.19–1.35) | 1.57 (0.64–3.83) | 0.566 |

DII®: dietary inflammatory index.
[1]: Adjustment for age.
[2]: Model 1: Additionally adjusted for height (continous), number of relatives with history of BC (3 categories), smoking status (never smoker, former smoker, current smoker), physical activity (METs-h/wk, continuous), alcohol intake (g/d, continuous), BMI (3 categories), age of menarche (5 categories), number of pregnancies of more than 6 months (continuous), pregnancy before the age of 30 years (dichotomous), months of breastfeeding (continuous), use of hormone replacement therapy (dichotomous) and its duration (continuous), and years at university (continuous).
Model 1a: Model 1 additionally adjusted for time since recruitment (continuous) and age of menopause (3 categories).
[3]: Model 2: Model 1 additionally adjusted for diabetes (dichotomous) and total energy intake (kcal/d, continuous).
Model 2a: Model 2 additionally adjusted for time since recruitment (continuous).

postmenopausal BC cases were included with 5512 healthy age-matched controls, aged 50–74 years. As in our study, they observed no significant associations (adjusted OR for the fifth vs. the first quintile: 1.01, 95% CI: 0.86–1.17) between the DII and post-menopausal BC. The association did not differ by estrogen receptor (ER) and progesterone receptor (PR) status (ER + PR+: adjusted OR for the fifth vs. the first quintile: 1.06, 95% CI: 0.88–1.27) (ER + or PR+: adjusted OR for the fifth vs. the first quintile: 1.07, 95% CI: 0.79–1.45) (ER- PR-: adjusted OR for the fifth vs. the first quintile: 0.87, 95% CI: 0.63–1.20). On the other hand, *Tabung et al.* assessed the association between DII and BC in the Women's Health Initiative (WHI) cohort. The analytic dataset from the WHI cohort comprised 122,788 postmenopausal women, among whom 7495 incident BC cases and 667 BC-related deaths were observed. In the first paper [52], *Tabung et al.* evaluated the association between DII and invasive BC incidence and death due to BC. Consistent with our results, no association was observed between DII and incident invasive BC cases (HR for the fifth vs. the first quintile: 0.99, 95% CI: 0.91–1.07), but they did observe that the more pro-inflammatory the diets were at baseline, the higher the risk of BC-related deaths (HR for the fifth vs. the first quintile: 1.33, 95% CI: 1.01–1.76). In their second paper [53], *Tabung et al.* evaluated the relationship between patterns of change in the inflammatory potential of diet and the risk of BC. They included 70,998 postmenopausal women from the WHI Observational Study and Dietary Modification trial control group and registered 3471 new invasive BC cases. Again, no significant association was observed between DII score or patterns of change in DII and overall invasive BC incidence (HR for the fifth vs. the first quintile: 1.03, 95% CI: 0.90–1.17); although they observed a significant nonlinear association between average adherence to the DII and ER-, PR- and HER2+ BC subtype (HR for the fifth vs. the first quintile: 2.37, 95% CI: 1.08–5.20). Similarly, *Zucchetto et al* [55] investigated the possible association between DII and the risk of dying from BC in an Italian retrospective cohort of 1453 pre- and post-menopausal women with BC, previously enrolled in a case-control study. They observed no significant associations between a higher adherence to the DII and BC specific mortality (HR third vs. first tertile: 0.97; 95% CI 0.73–1.27).

By contrast, there is evidence suggesting a direct association between lower DII scores and BC. Accordingly, in a Swedish cohort of 49,258 pre- and post-menopausal women, among whom 1895 incident BC cases were identified [57], a positive association between DII scores and incident BC (HR Q4 vs. Q1: 1.22, 95% CI: 1.00–1.39) was observed. The association was strongest among postmenopausal women (HR Q4 vs. Q1: 1.22, 95% CI: 1.01–1.46). Additionally, in a case-control study on the relationship between DII scores and BC in an Italian population composed of pre- and post-menopausal women [56], 2569 incident BC cases and 2588 controls were evaluated. It was observed that as DII scores increased, so, too, did the odds of having a BC diagnosed (odds ratio (OR) fifth vs. first quintile: 1.75, 95% CI: 1.39–2.21). Finally, in the Iowa Women's Health Study [58], the association between DII and risk of postmenopausal BC was prospectively evaluated. This cohort included 34,700 women aged 55–69 years old, followed up for 25 years, with 2910 incident BC. They found a positive association between DII score (indicating a more por-inflammatory diet) and incident BC cases (HR for DII third vs. first tertile: 1.11, 95% CI: 1.00–1.22), especially among obese women (HR for DII third vs. first tertile: 1.35, 95% CI: 1.00–1.66). Although our point estimates suggest a direct association between adherence to the DII score and the risk of BC, the confidence interval was wide; and, therefore, we observed no statistically significant associations.

Recently, in a case-control study among Chinese women (pre- and post-menopausal) with 867 BC cases and 824 controls, *Huang*

**Table 5**
Hazard ratio (IC 95%) of confirmed breast cancer cases for each quartile of DII® in the SUN Project among pre- and post-menopausal women.

| Variable | Quartiles of DII score | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | P for trend |
| | Most anti-inflammatory | | | Most pro-inflammatory | |
| Premenopausal breast cáncer | | | | | |
| N | 2244 | 2355 | 2377 | 2440 | |
| Cases | 14 | 12 | 14 | 17 | |
| Person-years of follow up | 20,019 | 21,415 | 21,345 | 22,662 | |
| Incidence rate/10,000 person-years | 6.99 | 5.60 | 6.56 | 7.50 | |
| Age adjusted HR[1] | 1 (ref) | 0.86 (0.40–1.85) | 1.03 (0.49–2.17) | 1.26 (0.62–2.56) | 0.411 |
| Model 1[2] | 1 (ref) | 0.80 (0.36–1.76) | 0.97 (0.45–2.06) | 1.14 (0.55–2.38) | 0.553 |
| Model 2[3] | 1 (ref) | 0.82 (0.37–1.81) | 0.98 (0.44–2.19) | 1.21 (0.51–2.87) | 0.527 |
| Postmenopausal breast cáncer | | | | | |
| N | 867 | 725 | 675 | 578 | |
| Cases | 11 | 9 | 3 | 11 | |
| Person-years of follow up | 5672 | 4357 | 4279 | 3390 | |
| Incidence rate/10,000 person-years | 19.39 | 20.65 | 7.01 | 32.45 | |
| Age adjusted HR[1] | 1 (ref) | 1.00 (0.41–2.42) | 0.34 (0.09–1.22) | 1.56 (0.67–3.63) | 0.436 |
| Model 1a[2] | 1 (ref) | 1.00 (0.41–2.45) | 0.33 (0.09–1.19) | 1.43 (0.59–3.44) | 0.604 |
| Model 2a[3] | 1 (ref) | 1.12 (0.45–2.79) | 0.39 (0.10–1.46) | 2.00 (0.71–5.64) | 0.304 |

DII®: dietary inflammatory index.
[1]: Adjustment for age.
[2]: Model 1: Additionally adjusted for height (continous), number of relatives with history of BC (3 categories), smoking status (never smoker, former smoker, current smoker), physical activity (METs-h/wk, continuous), alcohol intake (g/d, continuous), BMI (3 categories), age of menarche (5 categories), number of pregnancies of more than 6 months (continuous), pregnancy before the age of 30 years (dichotomous), months of breastfeeding (continuous), use of hormone replacement therapy (dichotomous) and its duration (continuous), and years at university (continuous).
Model 1a: Model 1 additionally adjusted for time since recruitment (continuous) and age of menopause (3 categories).
[3]: Model 2: Model 1 additionally adjusted for diabetes (dichotomous) and total energy intake (kcal/d, continuous).
Model 2a: Model 2 additionally adjusted for time since recruitment (continuous).

*et al* [54] observed a positive association between higher DII score and BC risk (adjusted OR Q4 vs Q1: 2.28, 95% CI: 1.71–3.03). They also performed some stratified analyses confirming this positive association in both premenopausal and postmenopausal women, ER+ and PR+, PR- and PR-, and normal weight, overweight or obese women. No significant association was observed between ER+ or EP+ (but not both) BC and DII score, or among underweight women. In contrast to all previously mentioned studies, this was the only previous study conducted in a non-European/or North American population.

Finally, a meta-analysis has been recently published by *Fowler et al*. [74], including all the published articles between 1980 and November 2016 where associations between DII and cancer had been studied. They concluded that a higher DII was associated with increased incidence of cancer (Relative Risk (RR): 1.25, 95% CI: 1.16–1.35), odds (OR: 1.75, 95% CI: 1.43–2.16) and mortality (RR: 1.67, 95% CI: 1.13–2.48) of all the included cancer types (including colorectal, breast, lung and prostate). Specifically, for BC the association remained significant (RR: 1.12, 95% CI: 1.03–1.22). These associations were consistent across different cancer types, populations and study designs.

We acknowledge that the present study has some limitations. First, we are aware that the number of incident cases of BC is limited which may compromise our statistical power. Our cohort is composed largely by young women and most of them are premenopausal, which reduces the number of incident BC cases. However, our point estimates are in the range of those observed in previous studies and these results are interesting interesting and novel, given that they can be included in future meta-analyses and provide new evidence for the first time from a Mediterranean country in the context of different food habits. Second, due to the small number of incident BC cases, we could not perform subgroup analyses by subtypes of BC cases. Associations between the DII® and some specific subtypes of BC have been previously reported. Third, dietary information was based on self-reported information. This might have led to some misclassification bias. Nevertheless, the food-frequency questionnaire had been previously validated [62] and the non-differential misclassification would bias our results towards the null value. Fourth, some of the information on BC incidence also was self-reported. In order to confirm the accuracy of the information, we asked our participants to send a copy of their medical reports. We run our analyses separately considering separately those cases which could be confirmed with the medical reports from those without any available medical report confirmation sent to the SUN Project as of the time of this analysis. In spite of this, we might have missed some cases of BC. This fact might have reduced the sensitivity to detect incident cases of BC. However, the close follow-up of our participants and the periodic consultation of the National Death Index will have limited the number of missed BC cases. Fifth, most of our participants consumed anti-inflammatory diets based on their DII® scores. This may reflect potential reporting bias by the participants. However, it is more likely to be explained by the fact that participants in the cohort have attended higher education institutions and are health-conscious volunteers who try to follow the Mediterranean diet with lower DII scores. In any case, the relatively narrow range of DII® values, especially the small percentage of participants with a pro-inflammatory DII, could have limited the variability in our exposure and, thus, may have hampered our ability to find statistically significant associations. Sixth, blood samples from our participants were not available. Therefore, we could not compare objective biomarkers of inflammation with the DII® in our cohort.

On the other hand, our study also shows some strengths. It is a dynamic cohort with more than 16 years of follow up, with 91% retention rate, and which includes actually 13,843 women. Also, we have an exhaustive information about the diet of the participants, collected by the food-frequency questionnaire mentioned before. Moreover, we have collected a wide array of potential confounders which have been included in the multivariable analyses, which reduces the room for residual confounding and other potential biases in our results.

## 5. Conclusions

Though results were suggestive of a positive relationship between DII scores and incident BC, we observed no significant association between the inflammatory potential of the diet and the risk of developing a BC in our cohort in the overall analysis and in subgroup analyses by menopausal status. More studies are needed to disentangle the association between the inflammatory potential of diet and the risk of BC, overall and for different subtypes of the disease and by menopausal status.

## Statement of authorship

IG and ET wrote the daft of the manuscript; IG, RSB, AR, NS and ET were responsible for data analysis; MRC, MAMG and ET were responsible for conception and design, data acquisition, and interpretation. All coauthors revised the manuscript critically for important intellectual content and approved the final version to be published.

## Conflict of interest

NS and JRH were supported by NIDDK award R44 DK103377.

JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the 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. NS is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

None of the other authors has conflicts of interest.

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