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Inflammatory potential of the diet and risk of breast cancer in the European Investigation into Cancer and Nutrition (EPIC) study

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Abstract

The role of chronic inflammation on breast cancer (BC) risk remains unclear beyond as an underlying mechanism of obesity and physical activity. We aimed to evaluate the association between the inflammatory potential of the diet and risk of BC overall, according to menopausal status and tumour subtypes. Within the European Prospective Investigation into Cancer and Nutrition cohort, 318,686 women were followed for 14 years, among whom 13,246 incident BC cases were identified. The inflammatory potential of the diet was characterized by an inflammatory score of the diet (ISD). Multivariable Cox regression models were used to assess the potential effect of the ISD on BC risk by means of hazard ratios (HR) and 95% confidence intervals (CI). ISD was positively associated with BC risk. Each increase of one standard deviation (1-Sd) of the score increased by 4% the risk of BC (HR = 1.04; 95% CI 1.01–1.07). Women in the highest quintile of the ISD (indicating a most pro-inflammatory diet) had a 12% increase in risk compared with those in the lowest quintile (HR = 1.12; 95% CI 1.04–1.21) with a significant trend. The association was strongest among premenopausal women, with an 8% increased risk for 1-Sd increase in the score (HR = 1.08; 95% CI 1.01–1.14). The pattern of the association was quite homogeneous by BC subtypes based on hormone receptor status. There were no significant interactions between ISD and body mass index, physical activity, or alcohol consumption. Women consuming more pro-inflammatory diets as measured by ISD are at increased risk for BC, especially premenopausal women.

Keywords Prospective study · Breast cancer · Inflammatory potential of the diet · Chronic inflammation

Abbreviations

BC	Breast cancer
BMI	Body mass index
CI	Confidence interval
DII	Dietary inflammatory index
EPIC	European prospective investigation into cancer and nutrition
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IARC	International agency for research on cancer
ICD-O	International classification of diseases for oncology
ISD	Inflammatory score of the diet
LR	Likelihood ratio
PR	Progesterone receptor
SD/Sd	Standard deviation

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Introduction

Inflammation is now widely accepted as one of the hallmarks of carcinogenesis, and chronic inflammation has been found to be associated with several cancers [1]. Regarding breast cancer (BC), the underlying mechanisms of inflammation are largely unknown. Inflammatory BC is a rare and aggressive disease, accounting for about 2–4% of all BC cases. It is defined by its clinical characteristics and, despite its name it does not show the histologic features of the inflammatory process [2]. The impact of chronic inflammation on BC risk is often assumed to have an indirect role, as one of the underlying pathways which may partially explain the causal association with obesity and physical activity [3, 4]. No dietary components other than alcohol have been found to be associated with BC risk with a convincing degree of evidence [4]. However, those for which a potential effect has been suggested (fats, foods containing carotenoids, non-starchy vegetables, fruit, and fibre) may be associated with inflammatory processes [5].

The relationship between the inflammatory potential of the diet and breast cancer has been evaluated through the Dietary Inflammatory Index (DII) in recent systematic reviews and meta-analyses [6–8]. Overall, evidence suggests that BC risk increases slightly with increasing DII scores, but this association is mainly driven by case–control studies, while summary estimates from cohort studies are either non-significant or marginally significant. Among the six prospective studies published so far [9–15] there are limitations that make it difficult to obtain a clear picture of the evidence. Some have a limited number of cases [12, 14], some focus on postmenopausal women [10, 11, 13] while others do not report the menopausal status of women [9, 12], and only two took into account different types of tumour according to the hormone receptor status [11, 15].

We aimed to assess the association between the inflammatory potential of the diet and risk of breast cancer in a prospective study in a European population. The large sample size of our study allowed us to assess differences of the association according to the menopausal status and hormone receptors status. Moreover, we considered the potential modifying effect of other lifestyle factors related to chronic inflammation.

Methods

Study population

The European Investigation into Cancer and Nutrition (EPIC) is a large prospective cohort study including over half a million participants recruited from ten European countries between 1992 and 2000. The study design, recruitment, follow-up procedures, and data collection have been described elsewhere [16]. In this work we had data available for the 351,284 women from nine out of the ten EPIC countries (Denmark, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). After excluding participants with prevalent cancers at recruitment, without data of follow-up or diagnosis, lacking dietary information or with implausible diet, a population of 318,686 women were included in this study (see details in the supplementary materials, Figure S1). All participants provided informed consent. The ethical committees from the International Agency for Research on Cancer (IARC) and from the participating centres approved the study.

Follow-up and ascertainment of breast cancer

In most countries, incident cancer cases and vital status were identified through a record linkage to regional or national registries. In France and Germany an active follow-up used a combination of cancer and pathology registries, health insurance records, and contacts with participants or their next-of-kin. BC cases were defined as tumours coded as C50.0–50.9 in the International Classification of Diseases for Oncology (ICD-O-2). Only primary malignant (invasive) tumours were considered; non-epithelial tumours or carcinoma in situ were excluded. Finally, 13,246 incident BC cases diagnosed during an average follow-up of 14 years were included in our analysis. Information on tumour receptor status was gathered on the basis of pathology reports. Information on oestrogen receptor (ER) and progesterone receptor (PR) status was available for 70% and 60% of cases respectively, whereas only 27% of cases had information on the human epidermal growth factor receptor 2 (HER2) status. Further information about geographical distribution and main features of cases is shown in Table S1.

Dietary and lifestyle data collection

Anthropometric data, blood samples and a lifestyle questionnaire including information on medical and reproductive history, sociodemographic characteristics, educational level attained, history of smoking habits, and physical activity were collected at recruitment. The participant's usual diet over the previous year was measured by country-specific food-frequency questionnaires or diet-history questionnaires. Energy, macro- and micronutrients, and other dietary components were calculated using country-specific food composition databases, which had been standardized across countries [17]. Furthermore, standardized 24-h dietary recalls were obtained from representative samples (5–12%) of each cohort to correct for systematic differences between the dietary questionnaires [18]. Sex- and country-specific

calibration models were applied to obtain individual predicted values of dietary intakes. The 24-h recall measurements were regressed on dietary intake from the questionnaire, including in the model total energy intake, age at recruitment, centre, education, smoking status, BMI, and physical activity. These models may be used to obtain predicted values (calibrated intake) of specific dietary items for all participants. A more detailed description of the procedure is shown in the supplementary material.

The inflammatory score of the diet (ISD)

To characterize the inflammatory potential of the diet we used an Inflammatory Score of the Diet (ISD) [19]. The ISD is initially based upon the DII. The DII is calculated using the intake of 45 dietary components (food, nutrients, or bioactive compounds) to which a weight has been assigned that reflects their degree of association with well-known inflammatory markers [20].

For the present study, a set of 27 food items (including macro- and micronutrients, other dietary components, and foods) available in the EPIC databases were used to calculate the ISD. Although we also had data on alcohol consumption, we decided to use a version of the ISD excluding alcohol, despite the anti-inflammatory weight of ethanol in the original DII [20]. A detailed description of the procedure is shown in the supplemental material (Table S2). Briefly, in order to calculate the individual ISD for each subject, the calibrated intake of each food item was standardized with the use of the mean and standard deviation (Sd) of our study population, and then converted to percentiles scores to avoid the right skewness of data and centred on 0 by doubling each percentile score and subtracting 1. These centred percentiles were multiplied by its corresponding inflammatory weight to obtain a specific ISD for each food item, which were summed to produce the overall ISD for each participant.

Owing to the way the ISD is calculated, its value indicates a more pro-inflammatory diet when is positive, while negative values correspond to a more anti-inflammatory diet. However, the weights to compute the score do not have units; they are only an indicator of the inflammatory potential of a singular dietary component. The value of the ISD for an individual must be interpreted as a relative index that allows the categorization of diets on a continuum scale from maximally anti-inflammatory to maximally pro-inflammatory.

Statistical analysis

We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% CIs for the association between BC risk and the inflammatory potential of the diet as measured by the ISD, with attained age as the underlying time scale. Cohort entry time was defined as age at recruitment, and exit time was considered age at diagnosis (cases), death, end of follow-up or last known contact, whichever occurred first. Proportional hazards assumptions were assessed by Schoenfeld residuals and were not significantly violated. All models were stratified by centre and age at recruitment (10-years categories) and adjusted for total energy intake.

A selection of potential confounders was done a priori, based on recognized risk factors of breast cancer available in our dataset. The multivariable model included the following covariates: educational level (none and primary school, technical/professional school, secondary school, university or higher and not specified), alcohol consumption (no consumption, < 5, 5–10, 10–20, 20–40, or > 40 g/day), physical activity (inactive, moderately inactive, moderately active, active and not specified), body mass index (BMI; < 25.0 and ≥ 25.0 kg/m^2), waist circumference (< 88 and ≥ 88 cm), menopausal status (pre-, peri- and postmenopausal), age at menopause (non-menopausal, < 45, 45–50, 50-5y or ≥ 55 years), number of live births (1, 2, 3, 4 or more), age at first birth (nulliparous, < 20, 20–30, and > 30 years), age at menarche (< 12, 12, 13 or > 13 years), breastfeeding (no, yes, or unknown), ever use of hormonal treatment (no, yes, or unknown), and ever use of oral contraceptives (no, yes, or unknown). An interaction term between menopausal status and BMI was also introduced to take into account the differential effect of excess body weight in BC risk before or after menopause. The ISD was both analysed as a categorical variable by quintiles using the lowest quintile as the reference category, and as a continuous variable using the standard deviation as unit of the ISD (i.e. the HR represents the increase in risk for 1-Sd increase of the ISD). Trend tests across quintiles of the ISD were calculated by entering the categorical variable into the model as a continuous term. The nonlinearity of the effect of the ISD on BC risk was assessed by adding a quadratic term to the model with the ISD as continuous variable and comparing the likelihood of the models with and without the quadratic term by means of the likelihood ratio (LR) test. The nonsignificant *P*-value was interpreted as an indication of a linear effect of the ISD on BC risk.

Separate analyses according to menopausal status were carried out. The menopausal status at recruitment was primarily based upon menstrual cycles over the past 12 months. Women were categorized as postmenopausal (no menstrual cycles), perimenopausal (1–9 menstrual cycles) or premenopausal (≥ 10 menstrual cycles). When data on menstrual status was lacking (about 1% of women) age cut-offs were applied as follows: premenopausal, < 42 years; perimenopausal, 42–55 years; postmenopausal, ≥ 55 years). Women with bi- or unilateral oophorectomy and/or hysterectomy (surgical menopause) were also classified as postmenopausal. To assess whether the association between BC risk and

ISD was different in pre-, peri- or postmenopausal women we used the likelihood ratio (LR) test of the interaction between ISD and menopausal status. The LR test of corresponding interactions with ISD was also used to evaluate the effect modification by BMI, waist circumference, physical activity, and alcohol consumption. The homogeneity of the risks of ISD by tumour receptor status was assessed by means of the Wald test.

We performed sensitivity analyses by excluding participants diagnosed during the first 2 years of follow-up to assess potential reverse causality caused by modification of dietary and lifestyle habits due to pre-existing subclinical conditions. Furthermore, the main Cox models (overall and by menopausal status) were repeated with additional adjustment for smoking to evaluate its potential confounding effect in the association of interest.

Results

The ISD, representing the inflammatory potential of the diet in our population (318,686 women) had a mean of 0.65 (Sd 1.59) and median of 0.80, ranging from − 5.45 (the maximum anti-inflammatory value) to 5.49 (the maximum pro-inflammatory value). The distribution of the baseline characteristics of the whole population and BC cases, together with the main parameters of the ISD are reported in Table 1; the ISD is described according to sociodemographic and lifestyle variables using the median, 25th and 75th percentiles, and age-, country- and energy-adjusted means (with 95% CIs) estimated by means of linear regression. Higher values of the ISD were observed in women between age 40–50 years, among highest alcohol consumers, women with 2 or ≥ 4 live births, women whose first birth was before age 20, having breastfed, and among those who used neither menopausal hormone treatment nor oral contraceptives. Decreasing trends of the ISD were observed with higher educational attainment, higher level of physical activity, lower BMI and lower waist circumference, younger age at menarche, and older age at menopause.

The association of the inflammatory potential of the diet with BC risk is presented in Table 2. The multivariable model showed positive association between higher values of the ISD and BC risk both with ISD as continuous ($HR_{1\text{-Sd increase}} = 1.04$; 95% CI 1.01–1.07) or categorical variable ($HR_{Q5vsQ1} = 1.12$; 95% CI 1.04–1.21) with a significant trend. A significant increase of BC risk with higher values of ISD was also evident in premenopausal and perimenopausal women (8% and 7% increased risk for 1-Sd increase of ISD respectively), while the association among postmenopausal women was not significant. However, the interaction between menopausal status and ISD was not significant (*P* value 0.09). No heterogeneity was observed in the association between ISD and BC risk according to different combinations of hormone receptor status. Despite some differences in the point estimates, the Wald test was consistently not significant.

Since body fatness, physical activity and alcohol consumption are well-established factors associated with BC and may contribute to low-grade chronic inflammation, we explored the association of the inflammatory potential of the diet with BC risk for different levels of these factors overall and separately in pre- and postmenopausal women (Table 3). For the sake of simplicity in the interpretation of results, perimenopausal women were excluded from this analysis. Overall, positive associations were observed for all categories, but significant associations (with ISD as continuous variable) were observed only among women with normal weight (HR = 1.05; 95% CI 1.01–1.09) and among inactive or moderately inactive women (HR = 1.06; 95% CI 1.02–1.10), and in nearly all categories of alcohol consumption. The same pattern with even higher estimates were observed among premenopausal women, with HR = 1.07 (95% CI 1.00–1.15) for women with normal weight, HR = 1.12 (95% CI 1.03–1.22) for inactive or moderately inactive women, and HR = 1.11 (95% CI 1.01–122) for non-to-low alcohol consumers (< 5 g/day). The picture was relatively similar for postmenopausal women though the point estimates were always weaker. It should be noted that the categories of women with normal weight and with moderate physical activity or inactive are those with the higher number of cases, so the significance may simply reflect a greater power. All the interactions were non-significant; therefore, from a statistical point of view there was no evidence of modification of the effect of ISD on BC risk by BMI, physical activity, or alcohol consumption, either overall or according to menopausal status.

Finally, the sensitivity analysis showed that the main associations observed were not substantially altered after excluding participants diagnosed during the first 2 years of follow-up in order to assess the possible reverse causality produced by any pre-diagnosis diet modification (Table 4). On the other hand, although tobacco smoking is not yet accepted as a cause of BC, a weak but significant association was observed in EPIC [21]. Therefore, we added tobacco smoking (status, time since quitting and intensity) to the multivariable model, but the pattern of associations remained largely unchanged.

Discussion

In this large cohort study, we observed a positive association between more pro-inflammatory diets and an increased risk of breast cancer, more pronounced in premenopausal women. Overall, women with the highest pro-inflammatory

Table 1 Main characteristics, number of events, and Inflammatory Score of the Diet (ISD) in the EPIC population (women)

	N	%	BC cases	ISD		*P* value
				Median (P_{25}, P_{75})	Mean (95% CI)[a]	
Age at recruitment (years)						< 0.001
< 40	38,464	12.1	664	− 0.42 (− 1.90–1.23)	0.54 (0.52–0.55)	
40 to < 50	104,598	32.8	3871	0.95 (− 0.19–1.94)	0.79 (0.78–0.80)	
50 to < 60	120,903	37.9	6204	0.88 (− 0.16–1.85)	0.58 (0.57–0.59)	
≥ 60	54,721	17.2	2507	0.89 (− 0.13–1.88)	0.67 (0.66–0.68)	
Educational level						< 0.001
None/primary	84,650	26.6	3276	1.56 (0.50–2.46)	1.07 (1.06–1.08)	
Technical	71,124	22.3	3027	1.05 (− 0.12–2.04)	0.76 (0.75–0.77)	
Secondary	76,461	24.0	3195	0.70 (− 0.31–1.56)	0.45 (0.44–0.46)	
Longer (including University)	73,408	23.0	3139	− 0.03 (− 1.19–0.99)	0.23 (0.22–0.24)	
Unknown	13,043	4.1	609	0.22 (− 0.83–1.19)	1.08 (1.06–1.10)	
Alcohol consumption (g/day)						< 0.001
Non-consumers	47,157	14.8	1695	1.28 (0.25–2.18)	0.78 (0.77–0.79)	
< 5	127,083	39.9	4854	0.90 (− 0.30–1.90)	0.62 (0.61–0.62)	
5 to < 10	52,151	16.4	2176	0.54 (− 0.65–1.60)	0.57 (0.56–0.58)	
10 to < 20	52,462	16.5	2395	0.52 (− 0.68–1.60)	0.62 (0.61–0.63)	
20 to < 40	30,790	9.7	1621	0.67 (− 0.39–1.65)	0.77 (0.76–0.79)	
≥ 40	9043	2.8	505	0.72 (− 0.31–1.70)	1.01 (0.98–1.03)	
BMI (kg/m^2)						< 0.001
< 18.5 (underweight)	6583	2.1	205	0.61 (− 0.74–1.62)	0.69 (0.66–0.72)	
18.5 to < 25 (normal weight)	184,406	57.9	7600	0.61 (− 0.56–1.61)	0.60 (0.60–0.61)	
25 to < 30 (overweight)	91,071	28.6	3936	1.08 (− 0.07–2.11)	0.71 (0.70–0.72)	
> 30 (obesity)	36,626	11.5	1505	1.20 (0.04–2.23)	0.82 (0.81–0.83)	
Waist circumference (cm)						< 0.001
< 88	176,585	55.4	7302	0.50 (− 0.81–1.65)	0.64 (0.63–0.64)	
≥ 88	48,275	15.1	2110	1.05 (− 0.10–2.08)	0.81 (0.80–0.82)	
Unknown	93,826	29.4	3834	1.13 (0.25–1.98)	0.63 (0.62–0.64)	
Height (cm)						< 0.001
Quartile1 (< 158)	82,930	26.0	3122	0.95 (− 0.12–1.92)	0.74 (0.73–0.75)	
Quartile2 (158–162.5)	76,802	24.1	3182	0.77 (− 0.36–1.80)	0.68 (0.67–0.69)	
Quartile3 (> 162.5–167)	82,297	25.8	3620	0.79 (− 0.37–1.83)	0.64 (0.63–0.65)	
Quartile4 (> 167)	76,657	24.1	3322	0.69 (− 0.61–1.78)	0.57 (0.56–0.58)	
Physical activity						< 0.001
Inactive	64,957	20.4	2666	1.18 (0.07–2.14)	0.99 (0.98–1.00)	
Moderately inactive	109,295	34.3	4708	0.68 (− 0.48–1.70)	0.59 (0.58–0.60)	
Moderately active	88,520	27.8	3600	0.83 (− 0.29–1.80)	0.59 (0.59–0.60)	
Active	50,163	15.7	2076	0.41 (− 0.80–1.55)	0.42 (0.41–0.43)	
Unknown	5751	1.8	196	1.93 (1.00–2.70)	1.42 (1.39–1.45)	
Age at menarche (years)						< 0.001
< 12	46,724	14.7	1914	0.64 (− 0.57–1.71)	0.59 (0.58–0.60)	
12	65,654	20.6	2766	0.73 (− 0.43–1.75)	0.62 (0.61–0.62)	
13	79,957	25.1	3353	0.74 (-0.43–1.79)	0.64 (0.63–0.64)	
> 13	115,619	36.3	4830	0.89 (− 0.26–1.90)	0.70 (0.69–0.70)	
Unknown	10,732	3.4	383	1.53 (0.65–2.24)	1.00 (0.97–1.02)	
Menopausal status						0.01
Premenopause	110,678	34.7	3297	0.53 (− 0.92–1.68)	0.67 (0.66–0.68)	
Perimenopause	62,796	19.7	2990	1.01 (− 0.02–1.95)	0.66 (0.65–0.67)	
Postmenopause	136,381	42.8	6597	0.91 (− 0.14–1.90)	0.66 (0.65–0.66)	

Table 1 (continued)

	N	%	BC cases	ISD		*P* value
				Median (P_{25}, P_{75})	Mean (95% CI)[a]	
Surgical menopause	8831	2.8	362	0.68 (− 0.37–1.65)	0.61 (0.59–0.64)	
Age at menopause (years)						< 0.001
< 45	16,821	5.3	628	1.01 (− 0.16–2.06)	0.68 (0.67–0.70)	
45 to 50	36,096	11.3	1594	1.00 (− 0.09–1.99)	0.68 (0.67–0.69)	
50 to 55	47,893	15.0	2288	0.92 (− 0.13–1.90)	0.61 (0.60–0.62)	
≥ 55	8947	2.8	528	0.78 (− 0.21–1.80)	0.52 (0.49–0.54)	
Unknown	35,455	11.1	1921	0.75 (− 0.21–1.71)	0.68 (0.67–0.69)	
Number of live births						< 0.001
0	46,826	14.7	1777	0.16 (− 1.37–1.43)	0.53 (0.52–0.54)	
1	47,019	14.8	2089	0.89 (− 0.24–1.89)	0.66 (0.65–0.68)	
2	121,629	38.2	5453	0.86 (− 0.24–1.86)	0.67 (0.66–0.67)	
3	57,390	18.0	2307	0.87 (− 0.23–1.87)	0.66 (0.65–0.67)	
4 or more	24,338	7.6	864	0.83 (− 0.29–1.86)	0.67 (0.65–0.68)	
Unknown	21,484	6.7	756	1.18 (0.17–2.05)	0.87 (0.85–0.89)	
Age at first birth (years)						< 0.001
Nulliparous	46,826	14.7	1777	0.17 (− 1.36–1.45)	0.52 (0.51–0.53)	
1st birth < 20	20,522	6.4	796	1.45 (0.26–2.43)	0.93 (0.91–0.94)	
1st birth 20–30	201,401	63.2	8415	0.85 (− 0.22–1.85)	0.67 (0.66–0.67)	
1st birth > 30	35,147	11.0	1698	0.67 (− 0.53–1.69)	0.57 (0.56–0.58)	
Unknown	14,790	4.6	560	1.17 (0.19–2.01)	0.86 (0.84–0.88)	
Breastfeeding						< 0.001
No	80,126	25.1	3334	0.47 (− 0.82–1.54)	0.62 (0.62–0.63)	
Yes	203,432	63.8	8648	0.85 (− 0.29–1.87)	0.64 (0.63–0.64)	
Unknown	35,128	11.0	1264	1.28 (0.29–2.11)	0.88 (0.86–0.89)	
Ever use of hormonal treatment						< 0.001
No	216,794	68.0	7889	0.78 (− 0.45–1.81)	0.66 (0.65–0.66)	
Yes	80,282	25.2	4482	0.76 (− 0.25–1.76)	0.63 (0.62–0.64)	
Unknown	21,610	6.8	875	1.36 (0.13–2.28)	0.80 (0.78–0.82)	
Ever use of contraceptive pill						< 0.001
No	120,803	37.9	5203	0.98 (− 0.10–1.97)	0.66 (0.66–0.67)	
Yes	189,455	59.4	7776	0.64 (− 0.57–1.70)	0.64 (0.63–0.64)	
Unknown	8428	2.6	267	1.63 (0.85–2.26)	1.07 (1.04–1.10)	

[a]Means (95% CI) adjusted by age, country, and energy intake, obtained from linear regression models

diets (fifth quintile of the ISD) had a significant increased risk of 12% compared with those with the most anti-inflammatory diets (first quintile). Each increase in 1 Sd of the index had a significant increased risk of 4%; rising to 8% among premenopausal women. This finding is particularly relevant for BC prevention since diet together with physical activity and weight control are key modifiable lifestyle factors, and BC is the most common cancer in women, with over 2 million new cases in 2018, and the leading cause of cancer death worldwide [22]. It is also worth noting that so far, no single dietary component apart from alcohol has been found to be a cause of BC with convincing degree of evidence [4]. On the contrary, looking at the totality of diet, as it is done by means of dietary patterns, it is likely to reflect an interactive, synergistic, and combined effect of dietary components [23]. Moreover, examination of diet as a whole can be more readily translated into dietary guidelines. In our population, a more anti-inflammatory diet is defined by a high consumption of legumes, vegetables, fruits (all kinds), and to a lesser extent, fruit and vegetable juices, coffee, and tea, as reflected by strong inverse correlation of these food group with ISD (Table S3). On the contrary, a more pro-inflammatory diet is characterized by high consumption of meat and meat products (including red and processed meat), foods rich in fats and oils, and sugar and confectionery.

To our knowledge the association between the inflammatory potential of the diet and BC risk has been assessed in six prospective studies. Our results are in line with those from

Table 2 Adjusted hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer by quintiles of the ISD

	Cases	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-trend	ISD continuous
Breast cancer (Global)								
Basic model[a]	13,246	Referent	1.01 (0.95–1.07)	1.04 (0.98–1.11)	1.05 (0.99–1.13)	1.09 (1.01–1.17)	0.012	1.03 (1.00–1.06)
Multivariable model[b]		Referent	1.01 (0.95–1.07)	1.05 (0.98–1.11)	1.06 (0.99–1.14)	1.12 (1.04–1.21)	0.002	1.04 (1.01–1.07)
Menopausal status[c]								
Premenopausal BC	3297	Referent	1.05 (0.93–1.19)	1.10 (0.97–1.25)	1.08 (0.94–1.25)	1.17 (0.99–1.38)	0.086	1.08 (1.01–1.14)
Perimenopausal BC	2990	Referent	1.00 (0.87–1.14)	1.01 (0.88–1.15)	1.09 (0.94–1.26)	1.23 (1.04–1.45)	0.008	1.07 (1.00–1.13)
Postmenopausal BC[d]	6959	Referent	0.99 (0.91–1.07)	1.04 (0.95–1.13)	1.04 (0.95–1.14)	1.06 (0.96–1.17)	0.149	1.02 (0.98–1.06)
P value for interaction[e]								0.091
BC by Hormone. receptors status[b]								
ER(+)	7508	Referent	1.02 (0.94–1.10)	1.06 (0.98–1.15)	1.06 (0.97–1.16)	1.14 (1.03–1.26)	0.012	1.04 (1.01–1.08)
ER(−)	1668	Referent	0.93 (0.79–1.10)	1.03 (0.87–1.22)	1.05 (0.87–1.26)	1.14 (0.93–1.41)	0.106	1.06 (0.98–1.15)
P-Wald test[f]								0.597
PR(+)	5080	Referent	1.00 (0.91–1.10)	1.02 (0.92–1.12)	1.06 (0.95–1.18)	1.15 (1.02–1.31)	0.024	1.05 (1.00–1.10)
PR(−)	2604	Referent	1.00 (0.87–1.14)	1.09 (0.95–1.25)	1.05 (0.90–1.22)	1.16 (0.98–1.39)	0.09	1.06 (0.99–1.13)
P-Wald test[f]								0.556
ER(+)PR(+)	4830	Referent	1.02 (0.92–1.12)	1.02 (0.92–1.13)	1.06 (0.95–1.19)	1.17 (1.03–1.33)	0.023	1.05 (1.00–1.10)
ER(−)PR(−)	1261	Referent	0.91 (0.75–1.09)	0.97 (0.80–1.17)	0.95 (0.77–1.18)	1.10 (0.86–1.40)	0.45	1.05 (0.95–1.15)
P-Wald test[f]								0.762
HER2(+)	861	Referent	1.16 (0.92–1.47)	1.25 (0.97–1.60)	1.10 (0.84–1.45)	1.07 (0.78–1.46)	0.872	1.00 (0.89–1.12)
HER2(−)	2670	Referent	0.99 (0.87–1.12)	0.98 (0.86–1.13)	1.00 (0.86–1.16)	1.22 (1.02–1.46)	0.1	1.05 (0.99–1.13)
P-Wald test[f]								0.391
Triple negative	320	Referent	0.96 (0.66–1.41)	1.06 (0.71–1.58)	1.07 (0.70–1.65)	1.12 (0.67–1.87)	0.565	1.13 (0.93–1.36)
Non-triple negative	2917	Referent	1.02 (0.90–1.16)	1.05 (0.92–1.20)	1.03 (0.89–1.19)	1.18 (1.00–1.40)	0.126	1.03 (0.97–1.10)
P-Wald test[f]								0.386

[a]Stratified by age and centre, and adjusted for energy intake

[b]Multivariable model: basic model further adjusted by educational level, alcohol consumption, BMI, physical activity, menopausal status, age at menopause, age at menarche, number of live births, age at first birth, breastfeeding, ever use of hormonal treatment, ever use of contraceptive pill, waist circumference, height and interaction between BMI and menopause

[c]Multivariable model: basic model further adjusted by educational level, alcohol consumption, BMI, physical activity, age at menopause (only in postmenopausal model), age at menarche, number of live births, age at first birth, breastfeeding, ever use of hormonal treatment (only in postmenopausal model), ever use of contraceptive pill, waist circumference and height

[d]This category includes women with natural menopause and surgical menopause

[e]*P* value for interaction is based upon the likelihood ratio (LR) test

[f]*P* value for the Wald test assessing the homogeneity of the relative risks

the Swedish Women's Lifestyle Health [9], in which there was significant increase of 4% of risk for each increase of one unit of the DII, as well as in the Iowa Women's Health study [13], with a marginally significant increased risk of BC of 11% for women in the highest tertile of the DII. The latter reported a significant interaction with BMI; the only significant increase in risk was observed among obese women. No association between DII and BC risk in postmenopausal women was found in the Women's Health Initiative [10], but an extended follow-up of the same study [11] reported a significant increased risk for women in the highest quintile of the DII limited to cases ER + PR + HER2+. The authors stated that it is no clear why a diet with high inflammatory potential would be associated with this specific subtype of BC. No association were found in small cohorts in France [12] and Spain [14]; but owing to the small sample size (158 and 100 BC cases respectively) both studies had little statistical power. The French study [12] reported a significant interaction with alcohol intake: DII was associated with increased BC risk in low-moderate drinkers but had a protective effect among heavier drinkers. According to authors the latter is unlikely to be causal. In this study the DII included alcohol intake and it is unclear how this may have affected the results. Finally, no association between DII and BC risk was observed in the Sister Study cohort [15] but in subgroup

Table 3 Adjusted hazard ratios (HR) and 95% confidence intervals (CI) of BC and ISD (continuous variable) among premenopausal and postmenopausal women and by subgroups of body mass index, physical activity and alcohol consumption

	All participants		Premenopausal[a]		Postmenopausal[b]	
	cases	HR (95% CI)[c]	cases	HR (95% CI)[c]	cases	HR (95% CI)[c]
BMI						
Underweight	205	1.16 (0.90–1.49)	58	1.51 (0.88–2.59)	81	0.96 (0.60–1.54)
Normal weight	7600	1.05 (1.01–1.09)	2242	1.07 (1.00–1.15)	3545	1.03 (0.98–1.09)
Overweight	3936	1.01 (0.96–1.06)	746	1.02 (0.90–1.16)	2372	1.00 (0.93–1.06)
Obesity	1505	1.06 (0.98–1.16)	251	1.17 (0.94–1.45)	961	1.04 (0.94–1.16)
Overweight + Obesity	5441	1.03 (0.98–1.07)	997	1.07 (0.96–1.19)	3333	1.02 (0.96–1.07)
P value for interaction[d]		0.257		0.133		0.740
P value for interaction[e]		0.303		0.345		0.554
P value for interaction[f]		0.772		0.743		0.470
Waist circumference						
< 88 cm	7302	1.03 (0.99–1.07)	2000	1.04 (0.97–1.12)	3917	1.02 (0.97–1.07)
≥ 88 cm	2110	1.01 (0.95–1.08)	325	1.20 (0.99–1.44)	1432	1.00 (0.92–1.09)
P value for interaction		0.158		0.250		0.218
Physical activity						
Inactive	2666	1.06 (0.99–1.13)	557	1.15 (0.98–1.34)	1685	1.04 (0.96–1.13)
Moderately inactive	4708	1.05 (1.00–1.11)	1095	1.10 (0.99–1.22)	2576	1.05 (0.98–1.12)
Moderately active	3600	1.02 (0.96–1.07)	1046	1.04 (0.93–1.16)	1560	0.98 (0.90–1.06)
Active	2076	1.04 (0.97–1.11)	528	1.02 (0.89–1.17)	1069	1.01 (0.93–1.11)
Inactive + Mod. inactive	7374	1.06 (1.02–1.10)	1652	1.12 (1.03–1.22)	4261	1.05 (1.00–1.10)
Active + Mod. active	5676	1.02 (0.98–1.07)	1574	1.03 (0.95–1.12)	2629	0.99 (0.93–1.05)
P value for interaction[g]		0.321		0.525		0.231
P value for interaction[h]		0.238		0.775		0.237
Alcohol consumption						
Non consumers	1695	1.02 (0.94–1.11)	399	1.09 (0.91–1.30)	924	0.99 (0.89–1.11)
Non-to-low consumers	6549	1.04 (1.00–1.08)	1682	1.11 (1.03–1.21)	3385	0.99 (0.94–1.05)
Consumers < 5 g/d	4854	1.04 (1.00–1.09)	1283	1.11 (1.01–1.22)	2461	0.99 (0.93–1.05)
Consumers ≥ 5 g/d	6697	1.05 (1.01–1.09)	1615	1.05 (0.97–1.13)	3574	1.06 (1.01–1.11)
P value for interaction[i]		0.992		0.637		0.556
P value for interaction[j]		0.944		0.819		0.482

[a]Multivariable model: stratified by age and centre, and adjusted for energy intake, educational level, alcohol consumption, BMI, physical activity, age at menarche, number of live births, age at first birth, breastfeeding, ever use of contraceptive pill, waist circumference and height

[b]Includes women with natural and surgical menopause. Multivariable model stratified by age and centre, and adjusted for energy intake, educational level, alcohol consumption, BMI, physical activity, age at menarche, number of live births, age at menopause, age at first birth, breastfeeding, ever use of contraceptive pill, ever use of hormonal treatment, waist circumference and height

[c]Hazard ratio (HR) and 95% confidence intervals (CI) for increase in one standard deviation (1-Sd) of the ISD

[d]*P*-value for interaction based upon the likelihood ratio (LR) test with BMI classified in 4 categories: underweight, normal weight, overweight and obesity

[e]*P* value for interaction based upon the likelihood ratio (LR) test with BMI classified in 3 categories: normal weight, overweight and obesity, excluding underweight

[f]*P* value for interaction based upon the likelihood ratio (LR) test with BMI classified in 2 categories: normal weight and overweight + obesity. Underweight were excluded from this test

[g]*P* value for interaction based upon the likelihood ratio (LR) test with physical activity classified in 4 categories: inactive, moderately inactive, moderately active and active

[h]*P* value for interaction based upon the likelihood ratio (LR) test with physical activity classified in 2 categories: inactive + moderately inactive and moderately active + active

[i]*P* value for interaction based upon the likelihood ratio (LR) test with alcohol consumption classified in 3 categories: non-consumers, consumers of < 5 g/d and consumers of ≥ 5 g/d

[j]*P* value for interaction based upon the likelihood ratio (LR) test with alcohol consumption classified in 2 categories: non-consumers + consumers of < 5 g/d (non-to-low consumers) and consumers of ≥ 5 g/d

Table 4 Sensitivity analysis. Association between breast cancer and the Inflammatory Score of the Diet (ISD) excluding the first 2 years of follow-up and an additional adjustment for smoking habits

	Cases	Quintiles of the ISD, HR (95% CI)[a]					*P*-trend	ISD continuous
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		HR (95%CI)
Excluding first 2 years follow-up[b]								
All breast cancer cases	11,794	Referent	0.99 (0.92–1.05)	1.03 (0.97–1.11)	1.06 (0.98–1.13)	1.11 (1.02–1.20)	0.003	1.04 (1.01–1.07)
Premenopausal breast cancers	2976	Referent	1.02 (0.90–1.15)	1.08 (0.94–1.24)	1.07 (0.93–1.25)	1.14 (0.96–1.35)	0.132	1.07 (1.01–1.14)
Premenopausal subgroups								
BMI: Normal weight	2015	Referent	1.01 (0.87–1.18)	1.05 (0.89–1.24)	1.09 (0.91–1.30)	1.13 (0.91–1.41)	0.2	1.08 (1.00–1.16)
PA: Inactive/ Mod. Inactive	1502	Referent	1.10 (0.92–1.33)	1.29 (1.06–1.58)	1.28 (1.03–1.59)	1.33 (1.04–1.71)	0.017	1.12 (1.03–1.21)
Alcohol: Non-to-low consumers	1512	Referent	0.95 (0.79–1.15)	1.07 (0.87–1.31)	1.09 (0.88–1.36)	1.27 (1.00–1.63)	0.025	1.11 (1.02–1.21)
Adjustment for smoking status[c]								
All breast cancer cases	13,246	Referent	1.00 (0.94–1.06)	1.04 (0.98–1.11)	1.05 (0.98–1.13)	1.10 (1.02–1.19)	0.009	1.03 (1.00–1.06)
Premenopausal breast cancers	3297	Referent	1.05 (0.93–1.18)	1.09 (0.96–1.24)	1.07 (0.93–1.24)	1.15 (0.97–1.36)	0.156	1.07 (1.01–1.13)
Premenopausal subgroups								
BMI: Normal weight	2242	Referent	1.05 (0.91–1.21)	1.04 (0.89–1.22)	1.08 (0.91–1.29)	1.13 (0.92–1.40)	0.286	1.07 (0.99–1.14)
PA: Inactive/ Mod. Inactive	1652	Referent	1.14 (0.95–1.36)	1.30 (1.08–1.58)	1.27 (1.03–1.57)	1.39 (1.09–1.77)	0.01	1.13 (1.04–1.22)
Alcohol: Non-to-low consumers	1682	Referent	0.99 (0.83–1.19)	1.10 (0.90–1.33)	1.09 (0.88–1.34)	1.29 (1.01–1.64)	0.031	1.11 (1.02–1.21)

[a]Multivariable model stratified by age and centre, and adjusted for energy intake, educational level, alcohol consumption, BMI, physical activity, age at menarche, number of live births, age at menopause, age at first birth, breastfeeding, ever use of contraceptive pill, ever use of hormonal treatment, waist circumference and height and interaction between BMI and menopause (overall model). Premenopausal: Multivariable model without the adjustment of menopause, age at menopause and ever use of hormonal treatment

[b]Multivariable model excluding participants with less than 2 years of follow-up

[c]Multivariable model with additional adjustment for smoking status and intensity, with the following categories: never smoker; current, 1–15 cigarettes/d; current, 16–25 cigarettes/d; current, > 25 cigarettes/d; former, quit ≤ 10 y; former, quit 11–20 y; former, quit > 20 y; or other smokers, including occasional smokers, exclusive smokers of cigar and/or pipe, and smokers with unknown status and/or unknown amount smoked

BMI body mass index, *PA* physical activity

analyses a significant increase of the DII was associated with risk of triple-negative BC.

The above-mentioned studies assessed the inflammatory potential of the diet by means of the DII, whereas we used the ISD. The two indices are quite similar; actually, we used the set of weights (inflammatory scores) of the DII to calculate the ISD. The major difference with respect to the DII was that the intake of each food item was standardized using the mean and standard deviation of the EPIC population instead of those from a regional worldwide database [20]. Furthermore, the Pearson's correlation coefficient between the ISD and the DII in the EPIC population was 0.91 (*P* value < 0.001) [19]. Therefore, although using slightly different methods to calculate the ISD and DII could be seen as a limitation when comparing our findings to those from previous studies, this does not pose a serious drawback to the comparability of the results.

In this work we used a version of the ISD excluding alcohol based on two main considerations. First, although ethanol has an anti-inflammatory weight in the original DII [20] it seems it is a dose-dependent effect. The negative relationship with inflammatory markers has been observed only among moderate alcohol consumers suggesting that the presence of other bioactive components in alcoholic beverages rather than ethanol itself may provide anti-inflammatory properties [24, 25]. Second, and even more relevant, is that alcohol is a well-established cause of breast cancer [3, 4]. If a negative association of an anti-inflammatory diet is found, recommendations for BC prevention based on our results would never include the consumption of alcohol. We used the same approach when we assessed the association of BC

with the adherence to a Mediterranean diet [26]. Anyway, it is also reassuring that a significant association between the ISD and BC risk was independent of the level of alcohol consumption (Table 3).

Hormones play an important role in BC risk and progression. There is a consistent link between postmenopausal concentrations of endogenous hormones (mainly oestradiol and testosterone) and increased BC risk. There seems to be a similar pattern in premenopausal women, but data are sparser [22]. On the other hand, adiposity and physical activity are both associated with chronic inflammation, which could partially explain the association of these factors with BC. While a state of low-grade chronic inflammation is induced by changes in the pathophysiology of adipokines of obese subjects [27], physical activity may reduce the macrophage production of inflammatory cytokines [28]. We have observed that the association of ISD with BC risk was particularly marked among premenopausal women and showed a consistent (and significant) association among inactive women and those with normal weight. Our results are compatible with the hypothesis that the potential effects of a pro- or anti-inflammatory diet are stronger, or at least more evident, among women for which hormonal pathways are less relevant and those without other strong determinants of systemic chronic inflammation.

A limitation of the present study is that the dietary exposure was derived from self-reported information relying on subjects' memory. Dietary assessment relying on the ability of individuals to recall a complex collection of data is known to contain measurement error. However, since diet was measured before disease occurrence, this error is nondifferential with respect to disease. The effect of random (nondifferential) misclassification is to increase the similarity between exposed and nonexposed groups, so that any true association between dietary exposure and outcome is diluted or underestimated. On the other hand, dietary information was gathered only once at recruitment. Repeated dietary assessments, which allows for a more accurate measure of dietary changes during follow-up, has often been recommended as an effective method of decreasing the measurement error; however, this needs to be considered having in mind the disease's latent period (the interval from when a cancer starts until it is diagnosed). In fact, the collected diet should correspond to the etiological relevant time window, assumed to take place before the onset of the disease. Further exposure afterwards, including the latency period, does not contribute to aetiology of the disease. In spite of the lack of precise knowledge of the natural history of breast cancer, a latency period of 16.3 years has been estimated recently [29]. In our study the average follow-up was 14 years; thus, the lack of repeated assessment of diet during follow-up does not appear to have induced any bias in the association between ISD and breast cancer risk.

Major strengths of this study are the prospective design and its large sample size, allowing sufficient statistical power for subgroup analyses. It is now widely accepted that the factors that modify the risk of BC are not the same when diagnosed before or after the menopause. On the other hand, the importance of distinguishing tumour subtypes according to hormone receptors when evaluation aetiology is now well established [30]. Therefore, the ability to assess within a common framework the associations between ISD and BC risk overall, as well as by menopausal status and tumour receptor status is an advantage.

In conclusion, our findings suggest that a more pro-inflammatory diet is associated with an increased risk of breast cancer, especially among premenopausal women. These results could help provide dietary recommendations, although they require further confirmation, for the prevention of breast cancer. In this line, it may be of interest to study new hypotheses regarding the possible effect of the inflammatory potential of the diet and the progression and prognosis of breast cancer.

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Declarations

Conflict of interest The authors have no conflict of interest to disclose.

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