Inflammatory Potential of the Diet and Risk of Breast Cancer in the European Investigation Into Cancer and Nutrition (EPIC) Study

Carlota Castro-Espin
Catalan Institute of Oncology: Institut Catala d' Oncologia https://orcid.org/0000-0001-9050-7590
Antonio Agudo (a.agudo@iconcologia.net)
Catalan Institute of Oncology: Institut Catala d' Oncologia
Catalina Bonet
Catalan Institute of Oncology: Institut Catala d' Oncologia
Verena Katzke
German Cancer Research Centre: Deutsches Krebsforschungszentrum
Renée Turzanski-Fortner
German Cancer Research Centre: Deutsches Krebsforschungszentrum
Krasimira Aleksandrova
German Institute of Human Nutrition
Matthias B Schulze
University of Potsdam: Universitat Potsdam
Anne Tjønneland
Danish Cancer Society: Kraeftens Bekaempelse
Christina C Dahm
Aarhus Universitet Health
José Ramón Quirós
Public Health Directorate, Asturias
María José Sánchez
Escuela Andaluza de Salud Pública, Granada
Pilar Amiano
Centro de Investigación Biomédica en red de epidemiologia y salud publica (CIBERESP)
María Dolores Chirlaque
IMIB Arrixaca: Instituto Murciano de Investigacion Biosanitaria Virgen de la Arrixaca
Eva Ardanaz
Navarra public health Institute, Pamplona
Giovanna Masala
Institute for Cancer Research, Prevention and Clinical Network -ISPRO, Florence,
Sabina Sieri
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano
Rosario Tumino
Cancer Registry and Histopathology Department, Provincial Health Authority, Ragusa,
Carlotta Sacerdote

Città della Salute e della Scienza University-Hospital Via Santena, Turin

Salvatore Panico

Federico II University: dipartamento di medicina Clinica e Chirurgia, Naples

Anne M May

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht

Stina Bodén

Department of Radiation Sciences, Oncology unit. Umeå University

Iger T Gram

Department of Community Medicine, University of Tromsø

Guri Skeie

Department of Community Medicine, University of Tromsø

Nasser Laouali

Paris-Saclay University, UVSQ

Sanam Shah

Paris-Saclay University, UVSQ

Gianluca Severi

Faculté de Médecine, Université Paris-Saclay, Inserm

Dagfinn Aune

Imperial College London Department of Epidemiology and Public Health: Imperial College London Department of Epidemiology and Biostatistics

Melissa A Merritt

Imperial College London Department of Epidemiology and Public Health: Imperial College London Department of Epidemiology and Biostatistics

Manon Cairat

Nutrition Métabolismes et Cancer: Nutrition Metabolismes et Cancer

Elisabete Weiderpass

International Agency for Research on Cancer, World Health Organization, Lyon

Elio Riboli

Imperial College London Department of Epidemiology and Public Health: Imperial College London Department of Epidemiology and Biostatistics

Laure Dossus

International Agency for Research on Cancer

Paula Jakszyn

Catalan Institute of Oncology: Institut Catala d' Oncologia

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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 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.

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, fruits 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, 15], some focus on postmenopausal women [10, 11, 13] while others do not report the menopausal status of women [9, 12], and only two take into account different types of tumour according to the tumour hormone receptor status [11, 14].

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) study 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 of EPIC 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 any prevalent cases 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-2). Only primary malignant (invasive) tumours were considered; non-epithelial tumours or carcinoma *in situ* were excluded. Finally, 13246 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. Standardized 24-h dietary recalls were obtained from representative samples (5–12%) of each cohort to correct for systematic differences between the dietary questionnaires [17]. Energy, macro- and micronutrients, and other dietary components were calculated using country-specific food composition databases, which had been standardized across countries [18].

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. 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 intake of each food item was first calibrated using data from 24-hr recall by an individual standardized with the use of the mean and standard deviation (Sd) of our study population, whereas the DII used an external worldwide database as a reference population. After normal-standardization, the intakes of each food item were multiplied by

its corresponding inflammatory weight to obtain a specific ISD for each food item, which are summed to produce the overall ISD for each participant. In this work we decided to use a version of the ISD excluding alcohol consumption, even though ethanol has an anti-inflammatory weight in the original DII [20].

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 upon recognized risk factors of breast cancer available in our dataset. The multivariable model included the following covariates: educational level, alcohol consumption, physical activity, body mass index (BMI), waist circumference, menopausal status, age at menopause, number of live births, age at first birth, age at menarche, history of breastfeeding, ever use of hormonal treatment and ever use of oral contraceptives. 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 obtained 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 of 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 with less than 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. 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.

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

			ISD			
	N	%	BC cases	Median (P_{25}, P_{75})	Mean (95 % CI)[1]	Pvalue
Age at recruitment, years						< 0.001
< 40	38464	12.1	664	-0.42 (-1.90–1.23)	0.54 (0.52–0.55)	
40 to < 50	104598	32.8	3871	0.95 (-0.19–1.94)	0.79 (0.78–0.80)	
50 to < 60	120903	37.9	6204	0.88 (-0.16–1.85)	0.58 (0.57–0.59)	
≥ 60	54721	17.2	2507	0.89 (-0.13–1.88)	0.67 (0.66–0.68)	
Educational level						< 0.001
None/Primary	84650	26.6	3276	1.56 (0.50–2.46)	1.07 (1.06–1.08)	
Technical	71124	22.3	3027	1.05 (-0.12–2.04)	0.76 (0.75–0.77)	
Secondary	76461	24.0	3195	0.70 (-0.31–1.56)	0.45 (0.44–0.46)	
Longer (including University)	73408	23.0	3139	-0.03 (-1.19–0.99)	0.23 (0.22–0.24)	
Unknown	13043	4.1	609	0.22 (-0.83–1.19)	1.08 (1.06–1.10)	
Alcohol consumption (g/day)						< 0.001
Non-consumers	47157	14.8	1695	1.28 (0.25–2.18)	0.78 (0.77–0.79)	
< 5	127083	39.9	4854	0.90 (-0.30–1.90)	0.62 (0.61–0.62)	
5 to < 10	52151	16.4	2176	0.54 (-0.65–1.60)	0.57 (0.56–0.58)	
10 to < 20	52462	16.5	2395	0.52 (-0.68–1.60)	0.62 (0.61–0.63)	
20 to < 40	30790	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)	184406	57.9	7600	0.61 (-0.56–1.61)	0.60 (0.60–0.61)	
25 to < 30 (overweight)	91071	28.6	3936	1.08 (-0.07–2.11)	0.71 (0.70–0.72)	
> 30 (obesity)	36626	11.5	1505	1.20 (0.04–2.23)	0.82 (0.81–0.83)	
Waist circumference, cm						< 0.001
< 88	176585	55.4	7302	0.50 (-0.81–1.65)	0.64 (0.63–0.64)	
≥ 88	48275	15.1	2110	1.05 (-0.10–2.08)	0.81 (0.80–0.82)	
Unknown	93826	29.4	3834	1.13 (0.25–1.98)	0.63 (0.62–0.64)	

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

				ISD		
Height, cm						< 0.001
Quartile1	82930	26.0	3122	0.95 (-0.12–1.92)	0.74 (0.73–0.75)	
Quartile2	76802	24.1	3182	0.77 (-0.36–1.80)	0.68 (0.67–0.69)	
Quartile3	82297	25.8	3620	0.79 (-0.37–1.83)	0.64 (0.63–0.65)	
Quartile4	76657	24.1	3322	0.69 (-0.61–1.78)	0.57 (0.56–0.58)	
Physical activity						< 0.001
Inactive	64957	20.4	2666	1.18 (0.07–2.14)	0.99 (0.98–1.00)	
Moderately inactive	109295	34.3	4708	0.68 (-0.48–1.70)	0.59 (0.58–0.60)	
Moderately active	88520	27.8	3600	0.83 (-0.29–1.80)	0.59 (0.59–0.60)	
Active	50163	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	46724	14.7	1914	0.64 (-0.57–1.71)	0.59 (0.58–0.60)	
12	65654	20.6	2766	0.73 (-0.43–1.75)	0.62 (0.61–0.62)	
13	79957	25.1	3353	0.74 (-0.43–1.79)	0.64 (0.63–0.64)	
> 13	115619	36.3	4830	0.89 (-0.26–1.90)	0.70 (0.69–0.70)	
Unknown	10732	3.4	383	1.53 (0.65–2.24)	1.00 (0.97–1.02)	

Table 1. *Continued*

				ISD		
	N	%	BC cases	Median (P_{25}, P_{75})	Mean (95 % CI)[1]	Pvalue
Menopausal status						0.01
Premenopause	110678	34.7	3297	0.53 (-0.92–1.68)	0.67 (0.66–0.68)	
Perimenopause	62796	19.7	2990	1.01 (-0.02–1.95)	0.66 (0.65–0.67)	
Postmenopause	136381	42.8	6597	0.91 (-0.14–1.90)	0.66 (0.65–0.66)	
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	16821	5.3	628	1.01 (-0.16–2.06)	0.68 (0.67–0.70)	
45 to 50	36096	11.3	1594	1.00 (-0.09–1.99)	0.68 (0.67–0.69)	
50 to 55	47893	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)	

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

				ISD		
Unknown	35455	11.1	1921	0.75 (-0.21–1.71)	0.68 (0.67–0.69)	
Number of live births						< 0.001
0	46826	14.7	1777	0.16 (-1.37–1.43)	0.53 (0.52–0.54)	
1	47019	14.8	2089	0.89 (-0.24–1.89)	0.66 (0.65–0.68)	
2	121629	38.2	5453	0.86 (-0.24–1.86)	0.67 (0.66–0.67)	
3	57390	18.0	2307	0.87 (-0.23–1.87)	0.66 (0.65–0.67)	
4 or more	24338	7.6	864	0.83 (-0.29–1.86)	0.67 (0.65–0.68)	
Unknown	21484	6.7	756	1.18 (0.17–2.05)	0.87 (0.85–0.89)	
Age at first birth, years						< 0.001
Nulliparous	46826	14.7	1777	0.17 (-1.36–1.45)	0.52 (0.51–0.53)	
1st birth < 20	20522	6.4	796	1.45 (0.26–2.43)	0.93 (0.91–0.94)	
1st birth 20–30	201401	63.2	8415	0.85 (-0.22–1.85)	0.67 (0.66–0.67)	
1st birth > 30	35147	11.0	1698	0.67 (-0.53–1.69)	0.57 (0.56–0.58)	
Unknown	14790	4.6	560	1.17 (0.19–2.01)	0.86 (0.84–0.88)	
Breastfeeding						< 0.001
No	80126	25.1	3334	0.47 (-0.82–1.54)	0.62 (0.62–0.63)	
Yes	203432	63.8	8648	0.85 (-0.29–1.87)	0.64 (0.63–0.64)	
Unknown	35128	11.0	1264	1.28 (0.29–2.11)	0.88 (0.86–0.89)	
Ever use of hormonal treatment						< 0.001
No	216794	68.0	7889	0.78 (-0.45–1.81)	0.66 (0.65–0.66)	
Yes	80282	25.2	4482	0.76 (-0.25–1.76)	0.63 (0.62–0.64)	
Unknown	21610	6.8	875	1.36 (0.13–2.28)	0.80 (0.78–0.82)	
Ever use of contraceptive pill						< 0.001
No	120803	37.9	5203	0.98 (-0.10–1.97)	0.66 (0.66–0.67)	
Yes	189455	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)	

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

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.

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[1]	13246	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[2]		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[3]								
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[4]	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[5]								0.091
BC by Hormone. receptors status[2]								
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[6]								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[6]								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)

	cases	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-trend	ISD continuous
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[6]								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[6]								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[6]								0.386

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

[2]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.

[3]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.

[4]This category includes women with natural menopause and surgical menopause.

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

[6]*P*-value for the Wald test assessing the homogeneity of the relative risks.

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 (< 5grams/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.

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[1]		Postmenopausal[2]	
	cases	HR (95% CI) [3]	cases	HR (95% CI)[3]	cases	HR (95% CI)[3]
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[4]		0.257		0.133		0.740
P-value for interaction[5]		0.303		0.345		0.554
P-value for interaction[6]		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)

	All participants		Premenopausal[1]		Postmenopausal[2]	
	cases	HR (95% CI) [3]	cases	HR (95% CI)[3]	cases	HR (95% CI)[3]
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[7]		0.321		0.525		0.231
P-value for interaction[8]		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 < 5g/d	4854	1.04 (1.00–1.09)	1283	1.11 (1.01–1.22)	2461	0.99 (0.93–1.05)
Consumers ≥ 5g/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[9]		0.992		0.637		0.556
P-value for interaction[10]		0.944		0.819		0.482

[1]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.

[2]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.

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

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

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

[6]*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.

[7]*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.

[8]*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.

	All participants		Premenopausal[1]		Postmenopausal[2]	
	cases	HR (95% CI) [3]	cases	HR (95% CI)[3]	cases	HR (95% CI)[3]
[9] *P*-value for interaction based upon the likelihood ratio (LR) test with alcohol consumption classified in 3 categories: non-consumers, consumers of < 5g/d and consumers of ≥ 5g/d.						
[10] *P*-value for interaction based upon the likelihood ratio (LR) test with alcohol consumption classified in 2 categories: non-consumers + consumers of < 5g/d (non-to-low consumers) and consumers of ≥ 5g/d.						

Finally, the sensitivity analysis showed that the main associations observed were not substantially altered after excluding participants with less than 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.

Table 4

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

		Quintiles of the ISD, HR (95% CI)[1]						ISD continuous
	cases	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-trend	HR (95%CI)
Excluding first 2 years follow-up[2]								
All breast cancer cases	11794	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)

[1]Multivariate 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.

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

[3]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.

		Quintiles of the ISD, HR (95% CI)[1]						ISD continuous
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[3]								
All breast cancer cases	13246	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)

[1]Multivariate 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.

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

[3]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.

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 diet (fifth quintile of the ISD) had a significant increased risk of 12% compared with those with the most anti-inflammatory diet (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 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 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 acknowledged 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 [15]; but with regard 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 [14] but in subgroup analyses significant associations were reported for postmenopausal women, obese women, and ER-PR- BC cases. Unfortunately, further details are not available since results of this study have been published only as an abstract.

All of the above-mentioned studies assessed the inflammatory potential of the diet by means of the DII, whereas we used the ISD. However, the results are comparable as the two indices are quite similar. Actually, for the calculation of the ISD we used the set of weights (inflammatory scores) proposed to calculate the DII. The major difference with respect to the DII was that the intake of each food items 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].

In this work we used a version of the ISD excluding alcohol based on two main considerations. First, although ethanol is considered to be anti-inflammatory in the original DII [20] it seems that alcohol has 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 we have only one assessment of diet carried out at recruitment, derived from self-reported information relying on subjects' memory. Therefore, measurement error cannot be discarded. However, since information was gathered before the identification of cases, such error would be non-differential, and hence it would most likely result in a decrease in true association. 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 [29]. 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.

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
standard deviation

Declarations

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Compliance with ethical standards

Conflict of interest

The authors have no conflict of interest to disclose.

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