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Association between the dietary inflammatory index and breast cancer in a large Italian case-control study

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Abstract

Introduction—The putative relationship between diet, including its inflammatory potential, and breast cancer has been studied extensively, but results remain inconsistent. Using data from a large Italian case-control study conducted between 1991 and 1994, we examined the association between the dietary inflammatory index (DII) and odds of breast cancer.

Methods—DII scores were computed using a validated 78-item food frequency questionnaire. Subjects were 2569 women with incident, histologically confirmed breast cancer and 2588 controls admitted to hospital for acute, non-hormone related diseases. Odds ratios (ORs) and 95% confidence intervals (CIs) based on continuous and quintiles of DII were estimated by multiple logistic regression adjusting for age, study centre, education, body mass index, parity, menopausal status, family history of hormone-related cancers and total energy intake.

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Author contributions: The authors' contributions were as follows: C.L.V., D.S., and M.M. designed and conducted the case-control study, V.R. created the dataset for analyses, N.S. calculated DII and conducted statistical analyses and wrote the first draft of the manuscript, J.R.H., C.L.V., and V.R. provided suggestions and revised the manuscript. All authors approved the final version of the manuscript.

Conflict of interest statement: None

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

Results—Women in quintiles 2, 3, 4 and 5 had ORs of breast cancer of 1.33 (95% CI: 1.11, 1.59), 1.37 (95% CI: 1.13, 1.66), 1.41 (95%CI: 1.15, 1.73) and 1.75 (95%CI: 1.39, 2.21), respectively, compared to women in quintile 1. One-unit increase in DII increased the odds of having breast cancer by 9% (95%CI: 1.05, 1.14).

Conclusions—A pro-inflammatory diet is associated to increased risk of breast cancer.

Introduction

Breast cancer is the most commonly diagnosed cancer and is the leading cause of cancer deaths in women worldwide [1],in Europe [2] and among Italian women, too [3]. The role of diet and inflammation in the etiology of breast cancer is unclear [4,5]; however, some evidence suggests an etiologic role for diet, in particular the ability of foods to modulate inflammation in the etiology of the disease [6,4].

Our body responds to any kind of tissue insult or injury with by releasing inflammatory cytokines, which leads to wound healing and successfully mounting an immune response to fight infections [7,8]. In contract to this acute response, chronic inflammation is a persistent state of low-grade inflammation in which tissue destruction and repair occur simultaneously over a long period of time, which may favour chronic diseases such as obesity, diabetes and cancer [9,10].

There is emerging evidence for the role of inflammatory cytokines and other factors that regulate inflammation in breast carcinogenesis [11–14]. These might modify the effect of hormonal factors that are related to breast cancer [11]. Specific dietary patterns and dietary components influence both inflammation [15–18] and breast cancer [19–22]. Because diet is a complex set of exposures that may interact, research on the possible effects of diet, inflammation and cancer occurrence is methodologically challenging [23].

The Dietary Inflammatory Index (DII) [24], was developed to measure the inflammatory potential of diet. It can be used in diverse populations to predict levels of inflammatory markers including C-reactive protein [25,26], interleukin-6 (IL-6) [27–29], and homocysteine [27]. The DII has been associated with risk of several cancers in cohort and case-control studies conducted worldwide [30–36] Previously, the DII has been shown to be associated with endometrial [34] and ovarian [33] cancers in Italy.

Thus far, the association between the DII and breast cancer incidence has been inconsistent. In a case-control study from Germany and a cohort from USA, no association was observed [5,37], while in a prospective study conducted in Sweden, increasing DII scores were found to be associated with breast cancer [4]. To test the dietary inflammation-breast cancer hypothesis, we examined the association between the DII and breast cancer in a large case-control study conducted in Italy [38]. Our working hypothesis is that women with breast cancer are more likely to have had a pro-inflammatory diet compared to women with no breast cancer.

Subjects and Methods

Design and Participants

We conducted a multicentric case–control study of breast cancer from June 1991 to April 1994 in six Italian areas: the provinces of Pordenone and Gorizia, the greater Milan area, the urban area of Genoa, the province of Forli, the province of Latina, and the urban area of Naples [38]. Cases were 2569 women with incident, histologically confirmed breast cancer (median age 55, range 23–74 years) admitted to major teaching and general hospitals of the study areas. Controls were 2588 women (median age 56, range 20–74 years) with no history of cancer admitted to the same hospitals for acute, non-neoplastic, non gynaecological conditions, unrelated to hormonal or digestive tract diseases and to diet. Among controls, 22% had traumas, 33% other orthopaedic diseases such as low back pain or strains, 15% acute surgical conditions, 18% eye diseases, and 12% other miscellaneous diseases. Less than 4% of cases and controls approached for interview did not consent to participate. The study was approved by the local ethics committees.

Cases and controls were interviewed in hospital by centrally trained interviewers, using a standard structured questionnaire. This included information on sociodemographic factors, anthropometric variables, lifestyle habits, as well as obstetric, gynaecologic, and general medical history.

A food frequency questionnaire (FFQ) was used to assess the subject's usual diet in the previous 2 years. Subjects were asked to indicate their average weekly consumption of 78 food items or food groups. Intakes lower than once a week, but at least once per month, were coded as 0.5/week. Nutrient and total energy intake was determined using an Italian food composition database [39,40]. The FFQ was tested for validity (7-day dietary record was used as reference method) [41] and reproducibility [42–44], and found to have satisfactory results for both validity and reproducibility.

In order to compute the DII score, dietary information for each study participant was first linked to the regionally representative database that provided a robust estimate of a mean and a standard deviation for each of the 45 parameters (i.e., foods, nutrients, and other food components) considered in the DII definition [24]. These parameters then were used to derive the subject's exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the parameter's standard deviation. The problems with right-skewing of z-scores was solved by converting them to percentiles. These were then centered on zero (indicated a null effect on inflammation) by multiplying by two and subtracting one. These additional steps assists with clinical interpretation because inappropriate weighting is avoided and higher (i.e., more positive) DII scores still represent more pro-inflammatory diets. The resulting value was then multiplied by the corresponding food parameter effect score (derived from a literature review on the basis of 1943 articles [24]).

All of these food parameter-specific DII scores were then summed to create the overall DII score for every subject in the study. Higher scores indicate a pro-inflammatory diet while lower scores indicate a more anti-inflammatory diet. The DII computed on this study's FFQ

includes data on 31 of the 45 possible food parameters comprising the DII: carbohydrates, proteins, fats, alcohol, fibers, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids (PUFA), omega 3, omega 6, niacin, thiamin, riboflavin, vitamin B6, iron, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, anthocyanidins, flavan3ols, flavonols, flavanones, flavones, isoflavones, caffeine, and tea. Because we adjusted for energy in the analyses, we did not use it for DII calculation. The remaining 13 missing food parameters are pepper, saffron, turmeric, garlic, ginger, onion, eugenol, trans fat, selenium, magnesium, vitamin B12, thyme and rosemary.

Statistical analysis

The DII was analysed both as a continuous variable and by quintiles of exposure computed among controls. Distributions of characteristics across quintiles of DII for controls were computed and differences were analyzed using the chi-square test. Odds ratios (ORs), and the corresponding 95% confidence intervals (CIs), were estimated using unconditional logistic regression models adjusted for quinquennia of age (categorically), total energy intake (quintiles among controls, categorically), study centre (categorically), education (<7, 7–11, ≥12 years, categorically), body mass index (BMI, <25, 25–<30, ≥30 kg/m^2, categorically), parity (0, 1–2, ≥3, categorically), menopausal status (pre/peri-menopause, post menopause), and family history of hormone-related cancers (no/yes). Missing values for adjustment variables were imputed to 7–11 years for education (14 cases and 23 controls), 25–<30 kg/m^2 for BMI (7 cases and 8 controls), 1–2 births for parity (3 cases and 2 controls), and post-menopausal status for menopausal status (3 cases) and then included in the models. Inclusion in the models of other variables, such as area, age at menarche, ever-use of oral contraceptives and hormone replacement therapy did not substantially modify any of the estimates and were not included to keep the most parsimonious model. The test for linear trend was carried out using the median value within each quartile as an ordinal variable. To investigate whether the effect of the DII was homogeneous across strata of selected covariates, we carried out stratified analyses according to age, BMI, parity, menopausal status, family history of hormone related cancers and energy intake. To test heterogeneity across strata, we computed the difference in the -2 log likelihood of the models with and without the interaction terms. Statistical analyses were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC).

Results

Cases were more highly educated than controls and tended to have lower parity, to be pre- or perimenopausal, and to report a history of hormone-related cancers in their family (data not shown)[45]. The overall mean DII and the corresponding standard deviation (SD) in this study is −0.39 ± 1.86, with a range from +5.14 (most pro-inflammatory score) to −6.18 (most anti-inflammatory score), Characteristics of women across quintiles of DII are provided for controls in Table 1. Women in the fifth quintile (representing a more pro-inflammatory diet) were significantly older, were more likely to be obese, be nulliparous, and have attained menopause.

Table 2 shows age-, centre- and energy-adjusted and multivariable-adjusted ORs of breast cancer according to the DII presented as quintiles and as continuous. In the multivariable-adjusted model, we found positive associations between DII and breast cancer risk, since women in quintiles 2, 3, 4 and 5 had 33% (OR:1.33; 95% CI: 1.11, 1.59), 37% (OR:1.37; 95% CI: 1.13, 1.66), 41% (OR:1.41; 95%CI: 1.15, 1.73) and 75% (OR:1.75; 95%CI: 1.39, 2.21) excess risk respectively compared to women in quintile 1 (P_{trend} <0.0001). When used as continuous, a one-unit increase in DII score (corresponding to 9% increase of its range in the current study) increased the OR of having breast cancer by 9% (OR:1.09; 95%CI: 1.05, 1.14) (Table 2).

Table 3 shows multivariable-adjusted ORs of breast cancer in strata of age, BMI, parity, menopausal status, family history of hormone related cancers and energy intake categories. Slightly stronger associations were observed between DII scores and breast cancer risk among post-menopausal women, with an 85% increased odds ((OR=1.85; 95% CI = 1.38, 2.48) compared to 60 % increased odds ((OR=1.60; 95% CI=1.08, 2,36) of breast cancer among pre/peri-menopausal women in the fifth quintile. However, the test for heterogeneity was not significant for any of the strata (*p* values >0.10).

Discussion

In this large Italian case-control study, we found a positive association between increasing DII score and odds of breast cancer. These results support our hypothesis that women consuming a more pro-inflammatory diet are at increased risk of breast cancer. The association of DII with breast cancer incidence is independent of effects of other risk factors such as age, BMI, menopausal status, parity, family history of hormone sensitive cancers and energy intake.

The association between diet and breast cancer has been explored previously in the same case-control study [38,46,47], with results showing negative associations with high intakes of fish and raw vegetables [47] and positive associations with a diet mainly based on bread, pasta [45], red and processed meat, and sugars [47]. In terms of nutrients, vitamin-D beta-carotene, vitamin E, calcium, PUFA, flavones and flavonols were associated with a reduced breast cancer risk [38,48,49,46]. Vitamin-D, beta-carotene, vitamin E, PUFA and flavanoids, which are part of the DII calculation, are anti-inflammatory components [24].

Others studies on diet and breast cancer have shown mixed results. Some studies have indicated that a Mediterranean diet and diets composed largely of vegetables, fruit, fish, and soy are associated with a decreased risk of breast cancer [50]. In the Iowa Women's Health study a protective role of vitamin D intake of >800 IU/day [51], and no association with a high-folate diet [52] and vitamins A, C and E [53]. In a meta-analyses of data from 21 prospective cohort studies, higher consumption of marine n-3 PUFA was associated with a lower risk of breast cancer [54]. A meta-analyses of 24 prospective cohort studies suggested that total dietary fat and specific fatty acids (apart from trans fats) might not be associated with increased risk of breast cancer [55].

The DII and breast cancer association has been explored in three previous studies. In a case-control study conducted in Germany, no significant association was observed between the DII score and postmenopausal breast cancer risk (adjusted $OR_{Q5\ vs\ Q1}$: 1.01, 95% CI: 0.86–1.17) [5]. In the Women's Health Initiative conducted in the US, DII scores were not associated with incidence of overall breast cancer (hazard ratio, HR_{Q5vsQ1}, 0.99; 95% CI, 0.91–1.07), whereas increasing DII was associated with a higher death from breast cancer (HR_{Q5vsQ1}, 1.33; 95% CI, 1.01–1.76) [56]. However, in a prospective study conducted in Sweden, a positive association was observed between DII scores and breast cancer risk ($HR_{\ DII\ quartile\ 4\ vs\ 1}$=1.18; 95% CI: 1.00, 1.39), which was evident in postmenopausal women only ($HR_{\ DII\ quartile\ 4\ vs\ 1}$=1.22; 95% CI: 1.01, 1.46) [4]. The mean DII scores in the Italian study were much more anti-inflammatory (−0.39±1.86) compared to the Swedish study (+2.67±1.47), and slightly more pro-inflammatory compared to the US study (−0.78±2.61). Energy adjusted DII scores were used in the German study and hence could not be directly compared. The positive association of the DII with breast cancer that we observed in this study may arise through the effect of a pro-inflammatory diet on levels of inflammatory cytokines, specifically IL-6, which is responsible for activation of the Stat3 pathway, induction of COOH terminal tensin-like (Cten) and increased expression of fascin, both important factors in breast cancer cell migration and invasion [57]. Increasing insulin levels and activation of insulin-like growth factor (IGF-1R), which are related both to IL-6 and diet, results in a chain of events that leads to inhibition of apoptosis and increased cell proliferation in breast tissue [58].

This study has the typical strengths and limitations characteristic of case-control studies [59,60], most notably information biases. Even though the information collected refers to the habitual diet in the 2 years before the diagnosis or hospital admission, dietary recall can be influenced by recent diagnosis of cancer; e.g., by confirmatory search. However, potential recall bias should be small, given the limited appreciation by the lay population in Italy of a link between diet and breast cancer risk at the time of this study. The dietary habits of hospital controls may differ from those of the general population, but we took great care to include as controls only patients admitted to hospital for acute conditions not related to major changes in diet and other life-style factors. Moreover, the same interview setting and catchment areas for cases and controls, and the almost complete participation rate are reassuring. Among the limitations of the study is the non-availability of 14 food parameters that could contribute to calculating the DII. The food parameters that are missing include turmeric, thyme, saffron and others. Food parameters such as turmeric and saffron are likely consumed in small amounts, infrequently or not consumed at all in this population; hence, their absence may not have had little impact on the scoring. However, missing information on food parameters such as garlic and onion are more likely to be consumed in this population and may have played a role in this association. Also, it should be noted that there was no drop off in predictive capacity of the DII when dropping from the maximum 45 parameters to 27 or 28 parameters into construct validation studies conducted in the US [25,28].

Among the strengths of this study are the uniquely large dataset, the satisfactory results on reproducibility [42–44] and validity [41]of the dietary questionnaire, and the ability to control for total energy intake and major potential confounding factors. In addition, no

significant heterogeneity was found across strata of BMI, parity, menopausal status, and other variables, providing further support to the consistency of the association observed between the DII and breast cancer risk.

In conclusion, women who consumed a more pro-inflammatory diet were at increased risk of breast cancer compared to women who consumed an anti-inflammatory diet. Our results provide evidence for the benefits of a diet high in food items that decrease inflammation and low in food items that increase inflammation.

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Table 1

Distribution of 2588 controls across quintiles of dietary inflammatory index (DII), Italy, 1991–1994.

Characteristics	DII quintiles					
	−6.18, −2.13	−2.12,−1.09	−1.08,−0.04	−0.03, 1.28	1.28, 5.14	*p* value[a]
	N (%)	N (%)	N (%)	N (%)	N (%)	
Age (years)						<0.0001
<45	104 (20.1)	102 (19.7)	99 (19.1)	92 (17.8)	75 (14.5)	
45–54	159 (30.7)	157 (30.3)	120 (23.2)	145 (28.0)	113 (21.9)	
55–64	151 (29.2)	158 (30.5)	178 (34.4)	152 (29.3)	163 (31.5)	
≥65	104 (20.1)	101 (19.5)	120 (23.2)	129 (24.9)	166 (32.1)	
Education (years) [b]						0.05
<7	316 (61.0)	282 (54.4)	318 (61.5)	323 (62.4)	330 (63.8)	
7–11	134 (26.1)	142 (27.6)	121 (23.6)	127 (24.8)	118 (23.0)	
≥12	63 (12.3)	91 (17.7)	73 (14.3)	61 (11.9)	66 (12.8)	
Body mass index (kg/m^2) [b]						0.03
<25	265 (51.5)	288 (55.6)	273 (52.9)	271 (52.2)	248 (48.2)	
25–30	177 (34.4)	168 (32.4)	163 (31.6)	148 (28.7)	188 (36.5)	
≥30	73 (14.2)	62 (12.0)	80 (15.5)	97 (18.8)	79 (15.3)	
Parity (number of births) [b]						0.009
0	62 (12.0)	60 (11.6)	74 (14.3)	86 (16.6)	98 (19.0)	
1–2	296 (57.1)	300 (58.0)	264 (51.2)	279 (53.9)	264 (51.1)	
≥3	160 (30.9)	157 (30.4)	178 (34.5)	153 (29.5)	155 (30.0)	
Menopausal status						0.0001
Pre/peri-menopause	201 (38.8)	184 (35.5)	167 (32.3)	155 (29.9)	135 (26.1)	
Post-menopause	317 (61.2)	334 (64.5)	350 (67.7)	363 (70.1)	382 (73.9)	
Family history of hormone-related cancers cancer						0.75

Characteristics	DII quintiles					*p* value[a]
	−6.18, −2.13	**−2.12, −1.09**	**−1.08, −0.04**	**−0.03, 1.28**	**1.28, 5.14**	
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
Yes	43 (8.3)	49 (9.5)	42 (8.1)	53 (10.2)	46 (8.9)	
No	475 (91.7)	469 (90.5)	475 (91.9)	465 (89.8)	471 (91.0)	

[a] *p* value from Chi-square test

[b] The sum does not add up to the total because of some missing values

Table 2

Odds ratios (ORs) of breast cancer and corresponding 95% confidence intervals (CIs) according to dietary inflammatory index (DII) among 2569 cases and 2588 controls. Italy, 1991–1994.

	DII quintiles, OR (95% CI)					*p* value for trend	DII continuous[d]
	−6.18, −2.13	**−2.12,−1.09**	**−1.08,−0.04**	**−0.03, 1.28**	**1.28, 5.14**		
Case/Controls	443/517	531/518	526/518	532/518	537/517		2569/2588
Model 1[a]	1 [b]	1.34 (1.12, 1.60)	1.33 (1.10,1.60)	1.36 (1.11, 1.65)	1.71 (1.36, 1.65)	<0.0001	1.09 (1.04, 1.13)
Model 2[c]	1 [b]	1.33 (1.11, 1.59)	1.37 (1.13, 1.66)	1.41 (1.15, 1.73)	1.75 (1.39, 2.21)	<0.0001	1.09 (1.05, 1.14)

[a] Adjusted for quinquennia of age, study centre, and energy intake.

[b] Reference category.

[c] Model 2 additionally adjusted for education, body mass index, parity, menopausal status and family history of hormone-related cancers.

[d] One unit increase equals 9% increase of its range in the current study (+5.14 to −6.18).

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Table 3

Odds ratios (ORs) of breast cancer and corresponding 95% confidence intervals (CIs) according to quintiles of dietary inflammatory index (DII), among 2569 cases and 2588 controls. Italy, 1991–1994.

	Cases/Controls [a]	DII quintiles, OR (95% CI)[b]					*p* value for trend	*p* value for interaction
		−6.18, −2.13	−2.12,−1.09	−1.08,−0.04	−0.03, 1.28	1.28, 5.14		
Age								0.62
<55 years	1242/1166	1 [c]	1.06 (0.82, 1.37)	1.38 (1.05, 1.81)	1.34 (1.01, 1.79)	1.76 (1.25, 2.47)	<0.001	
≥55 years	1327/1422	1[c]	1.67 (1.28, 2.16)	1.34 (1.02, 1.76)	1.48 (1.11, 1.98)	1.76 (1.28, 2.42)	0.01	
BMI								0.38
<25kg/m^2	1392/1345	1[c]	1.20 (0.93, 1.54)	1.34 (1.03, 1.75)	1.40 (1.06, 1.86)	1.61 (1.16, 2.22)	0.002	
≥25kg/m^2	1170/1235	1[c]	1.51 (1.15, 1.98)	1.39 (1.05, 1.85)	1.41 (1.05, 1.91)	1.90 (1.36, 2.66)	0.25	
Parity								0.48
Nulliparous	401/380	1[c]	1.31 (0.77, 2.22)	1.67 (0.98, 2.83)	1.44 (0.83, 2.52)	1.78 (0.96, 3.31)	0.04	
Parous	2165/2206	1[c]	1.34 (1.10, 1.63)	1.32 (1.07, 1.62)	1.44 (1.16, 1.80)	1.78 (1.39, 2.29)	0.10	
Menopausal status								0.71
Pre/peri-menopause	987/842	1[c]	1.08 (0.81, 1.45)	1.43 (1.05, 1.95)	1.48 (1.06, 2.06)	1.60 (1.08, 2.36)	0.52	
Post-menopause	1579/1746	1[c]	1.51 (1.19, 1.91)	1.34 (1.04, 1.72)	1.40 (1.08, 1.82)	1.85 (1.38, 2.48)	0.007	
Family history of female-hormone related cancers								0.98
Yes	396/233	1[c]	1.44 (0.82, 2.51)	1.37 (0.75, 2.49)	1.12 (0.61, 2.05)	1.85 (0.89, 3.81)	0.30	
No	2173/2355	1[c]	1.32 (1.08, 1.60)	1.34 (1.10, 1.65)	1.43 (1.15, 1.77)	1.74 (1.36, 2.23)	0.03	
Energy intake[d]								0.11
<2081 kcal	1405/1294	1[c]	1.26 (0.98, 1.61)	1.17 (0.91, 1.50)	1.24 (0.96, 1.61)	1.25 (0.95, 1.64)	0.17	
≥2081 kcal	1164/1294	1[c]	1.12 (0.85, 1.47)	1.23 (0.94, 1.61)	1.27 (0.98, 1.64)	1.30 (1.01, 1.67)	0.03	

[a] The sum may not add up to the total because of some missing values.

[b] Adjusted for quinquennia of age, study centre, energy intake, education, body mass index, parity, menopausal status and family history of hormone-related cancers, when appropriate.

[c] Reference category.

[d] Median energy intake among controls.