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A higher Dietary Inflammatory Index score is associated with a higher risk of breast cancer among Chinese women: a case–control study

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Abstract

Previous studies have investigated the association between dietary inflammatory potential and the development of cancer. For breast cancer the results have been equivocal. The present study aimed to investigate whether higher Dietary Inflammatory Index™ (DII) scores were associated with increased risk of breast cancer among Chinese women. A total of 867 cases and 824 controls were recruited into the present case–control study from September 2011 to February 2016. DII scores were computed based on baseline dietary intake assessed by a validated 81-item FFQ. The OR and 95 % CI were assessed by multivariable logistic regression after adjusting for various potential confounders. DII scores in this study ranged from −5·87 (most anti-inflammatory score) to +5·71 (most proinflammatory score). A higher DII score was associated with a higher breast cancer risk (adjusted $OR_{quartile\ 4\ v.\ 1}$ 2·28; 95 % CI 1·71, 3·03; adjusted $OR_{continuous}$ 1·40; 95 %CI 1·25, 1·39). In stratified analyses, positive associations also were observed except for underweight women or women with either oestrogen receptor+ or progesterone receptor+ status (but not both). Results from this study indicated that higher DII scores, corresponding to more proinflammatory diets, were positively associated with breast cancer risk among Chinese women.

Key words: **Dietary Inflammatory Index: Inflammation: Breast cancer: Case–control studies**

China has a low incidence of breast cancer, though since the 1990s incidence has increased more than twice as fast as have the global rates[1]. According to cancer statistics for China in 2015, breast cancer alone is expected to account for 15 % of all new cancers in women and is the leading cause of cancer death in women younger than 45 years[2]. Although acute inflammatory response is needed for mounting a normal immune response, chronic inflammation is known to be associated with common epithelial cancers, including breast cancer[3]. Although dietary factors have been shown to be related to chronic inflammatory states, which play an important role in breast cancer development, there is little evidence of the proinflammatory and anti-inflammatory effects of the overall diet on breast cancer risk[4,5].

It is known that mediators and cellular effectors of inflammation are important constituents of the tumour microenvironment[6]. Inflammation has been suggested as an important player in breast cancer initiation, promotion and metastasis, all phases in

Abbreviations: CRP, C-reactive protein; DII, Dietary Inflammatory Index; ER, oestrogen receptor; PR, progesterone receptor.

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which cytokines are prominent players[7]. A number of studies indicate that the levels of inflammatory cytokines, particularly C-reactive protein (CRP), are associated with breast cancer development[8–10]. CRP is a classical acute phase reactant protein from the pentraxin family; and a moderate rise in CRP level is seen in chronic inflammatory states[11]. IL-6 is involved in the Stat3 pathway, which results in the induction of carboxylic acid terminal functional group and increased expression of fascin, both of which play an important role in breast cancer cell migration and invasion[12].

To date, the association between diet and inflammatory states has been explored with respect to foods, nutrients and dietary patterns. For instance, fibre, PUFA, vitamin C/E, fruit and vegetable intake, Mediterranean diet pattern and low-glycaemic index diet are associated with lower levels of chronic inflammation[4,5,13–16]. In contrast, red meat and butter intake, SFA and a Western dietary pattern appear to increase levels of high-sensitivity CRP (hs-CRP) and proinflammatory interleukins which are used as markers of inflammation[4,5,17].

The Dietary Inflammatory Index™ (DII), originally developed by Cavicchia *et al.*[18] and updated by Shivappa *et al.*[19] in 2014 at the University of South Carolina, is a literature review-based score that reflects the potential inflammatory effects of the diet. Previous studies have been performed to evaluate the associations between the DII score and cancer risk, including colorectal cancer, ovarian cancer and breast cancer[20–32]. To date, six studies drawing mixed conclusions have been conducted to investigate the association between DII scores and breast cancer risk in Europe and the USA[27–32]. In addition, no study has been performed in Asia, where dietary patterns are different from those of Europe and North America.

The aim of the present study was to investigate whether individual diets based on their inflammatory potential effects, as indicated by their DII scores, were associated with breast cancer risk. Our hypothesis was that a higher DII score (indicating a proinflammatory diet) increases the risk of breast cancer.

Methods

Study subjects

This is an ongoing case–control study begun in September 2011. Potential cases were recruited among patients who were admitted to the surgical units of three teaching and general hospitals in Guangzhou, China from September 2011 to February 2016. Eligible subjects were female, aged 25–70 years and natives of the province of Guangdong or having lived in Guangdong for at least 5 years, with incident, primary, histologically confirmed breast cancer diagnosed no more than 3 months before the interview. Women were excluded if they could not understand or speak Mandarin/Cantonese or had a prior history of breast cancer or other cancers. A total of 867 cases out of 955 eligible women (90·8 %) participated in this study.

Controls were patients with no history of cancer and admitted to the same hospitals during the same time period as the cases. They were frequency matched by age (5-year interval) to the case patients. They were selected from the departments of Ophthalmology, Plastic and Reconstructive Surgery, Vascular Surgery, Ear-Nose-Throat and Orthopaedics and Microsurgery. A total of 824 (91·6 %) controls out of 900 eligible controls participated in this study.

We assumed that people with higher DII score represented 25 % of the general population, the estimated OR between the DII score and breast cancer risk was 1·41[11], the type I error rate was <0·05 ($\alpha = 0{\cdot}05$), the power of test was 80 % ($\beta = 0{\cdot}20$) and the response rate was 90 %. Based on these assumptions, we require a sample size of 762 cases.

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human subjects were approved by the ethical committee of School of Public Health, Sun Yat-sen University. Written informed consent was obtained from all participants before the interview.

Data collection

All study participants completed a face-to-face interview conducted by trained interviewers using a structured questionnaire to collect information on dietary habits and potential confounding factors.

The core questionnaire was used to collect information on socio-demographic factors, body weight and height, lifestyle factors (e.g. active and passive smoking, alcohol drinking and physical activity), menopausal status and reproductive history and family history of cancer. In this study, regular smokers were defined as someone smoking at least one cigarette a day for more than 6 consecutive months. Passive smoking meant to be exposed to others' tobacco smoke for at least 5 min/d in the previous 5 years. Regular drinking was defined as alcohol drinking at least once per week in the past year. Postmenopausal status was defined as at least 12 months since the last menstrual cycle. BMI was calculated by dividing weight (kg) by height (m^2) squared. In addition, leisure-time physical activity was measured. Relevant medical information, medical diagnosis, histological findings and oestrogen receptor (ER) and progesterone receptor (PR) status were abstracted from the hospital medical records.

An 81-item FFQ was used to collect data on food consumption. Participants were asked to report information on frequency of intake and portion size during the preceding 12 months before diagnosis for cases or interview for controls. From these data the average intake of each food item in g/d were calculated. Food photographs were used to help participants quantify the portions consumed. Information on frequency of intake and portion size was used to calculate the amount of each food item consumed on average (g/d). Total energy and intakes of specific nutrients were computed based on the 2002 Chinese Food Composition Table[33].

Calculation of the Dietary Inflammatory Index score

The original DII was developed by Cavicchia *et al.*[18] and updated by Shivappa *et al.*[19] and the calculation process was documented elsewhere. Hs-CRP measurements were used to examine construct validity of the DII in a longitudinal cohort

using DII scores derived from 24-h dietary recall interviews and 7-d dietary recalls. In the updated version, 1943 articles were reviewed and scored. In all, forty-five food parameters, including foods, nutrients and other bioactive compounds, were evaluated based on their inflammatory effect on six specific inflammatory markers, such as CRP, IL-1β, IL-4, IL-6, IL-10 and TNF-α. A world database based on food consumption from eleven populations globally represented global daily intake for each of the forty-five parameters (i.e. foods, nutrients and other food components). This was used as standard dietary intake reference to standardise DII scores to global norms. A standard mean for each parameter from the representative world database was subtracted from the actual individual exposure and divided by its standard deviation to generate z scores. These z scores were converted to percentiles (minimising effects of outliers/right- skewing), then doubled the value and subtracted 1 to achieve symmetrical distribution with values centred on 0. The resulting value was then multiplied by the corresponding inflammatory score for each food parameter and summed across all food parameters, in order to obtain the overall DII score. The inflammatory score for each food parameter derived from a literature review on the basis of 1943 articles representing studies of different design on diet and inflammation. Overall, thirty-three of the forty-five possible food parameters used for the DII calculation were available in this study, and these food parameters were vitamin B_{12}, vitamin B_6, β-carotene, carbohydrate, cholesterol, fat, fibre, folic acid, garlic, Fe, Mg, MUFA, niacin, n-3 fatty acids, n-6 fatty acids, onion, protein, PUFA, riboflavin, SFA, Se, thiamin, vitamin A, vitamin C, vitamin E, Zn, flavan-3-ol, flavones, flavonols, anthocyanidins, isoflavones and pepper. We calculated the DII score based on energy-adjusted intake of the thirty-three single food parameters using the energy density approach which calculated per 4184 kJ (1000 kcal) of energy[34]. As the original construct validation, the new DII also was validated in four studies in different populations with an extended number of inflammatory biomarkers (e.g. IL-6, hs-CRP, and TNF-α)[35–38].

Statistical analysis

The DII score was categorised into quartiles based on the distribution among the controls. The DII was analysed both as a continuous variable (i.e. a one-unit increment in the DII corresponds to approximately 12 % of its global range) and by quartiles of exposure. The lowest quartile of DII scores served as the reference group in the analyses. Student's t test, one-way ANOVA test and Kruskal–Wallis tests were used for continuous variables and χ^2 test were used for categorical variables to test differences between different groups. OR and 95 % CI summarising the association between breast cancer risk and the DII score were calculated by using unconditional logistic regression. The following variables were adjusted in the logistic regression models: education, income, passive smoking, BMI, first-degree relative with cancer and history of benign breast disease. Confounding factors were selected by comparing baseline characteristics between the cases and controls. Tests for trend were performed by entering the categorical variables as continuous parameters in the models.

In China, BMI < 18·5 kg/m^2 was defined as underweight, BMI ≥ 18·5 and <24 kg/m^2 as normal weight, BMI ≥ 24 and <28 kg/m^2 as overweight and BMI ≥ 28 kg/m^2 as obese[39]. Analyses stratified by BMI (underweight, normal weight, overweight and obese) were conducted. Moreover, stratified analyses by menopausal status (premenopausal and postmenopausal) and sex hormone status (ER-positive (ER+), or ER-negative (ER−); PR-positive (PR+) or PR-negative (PR−)) also were conducted. The significance level was set at 0·05 (two-sided). All of the aforementioned statistical analyses were performed using SPSS® 13.0 (SPSS Inc.).

Results

The comparison of baseline characteristics between cases and controls is shown in Table 1. Compared with controls, breast cancer cases were more likely to have lower levels of education and income. Compared with controls, more cases reported having a first-degree relative with cancer, a history of benign breast disease and a higher BMI. A higher proportion of cases tended to smoke regularly and be exposed to second-hand smoke. All of the above-referenced variables were considered potential confounders and adjusted for in the subsequent multivariable analyses. No significant differences were observed between cases and controls on age, occupation, marital status, physical activity, alcohol drinking, age at menarche, age at first live birth, menopausal status, parity, breast-feeding history, ever use of oral contraceptive or hormone replacement therapy.

The DII score in this study ranged from −5·87 (most anti-inflammatory score) to +5·71 (most proinflammatory score) and the mean DII score −1·48 (SD 1·78). For cases, the mean DII was −1·75 (SD 1·66), and it was −1·23 (SD 1·86) for controls. Intakes of thirty-three dietary nutrients available in the calculation of DII are presented in Table 2. A higher DII score was significantly associated with higher intake of SFA and distributions of some nutrients (total fat, folic acid, Fe, n-6 fatty acids, PUFA, vitamin A) were significantly different across quartiles of DII score. Total fat intake in the 3rd quartile of DII score was lower than that observed in any other quartile; the highest folic acid intake was in the 2nd quartile, whereas the lowest intake was observed in the 3rd quartile. The highest vitamin A intake was in the 2nd quartile, whereas the lowest intake was in the 4th quartile. Fe intake in the 4th quartile was the lowest and medians of intake in other quartiles were equal, which was the same distribution as PUFA; n-6 fatty acid intake was highest in the 4th quartile.

More control subjects in the 1st quartile of DII scores were exposed to passive smoking than in any other quartile. More case subjects in the 4th quartile of DII score had a first-degree relative with cancer than observed in any other quartile. All other distributions of characteristics among case or control subjects were not significantly different across quartiles of DII (online Supplementary Tables S1 and S2).

The association between the DII and breast cancer risk is shown in Table 3. When analyses were carried out using continuous DII, a significant positive association between breast cancer risk and the DII score was observed (crude OR 1·36; 95 % CI 1·23, 1·51; adjusted OR 1·40; 95 % CI 1·25, 1·39). When fitted as quartiles, there was a trend of increasing risk for

Table 1. Characteristics data of breast cancer cases and matched controls in a Chinese case–control study, 2011–2016
(Mean values and standard deviations; numbers and percentages)

	Cases (*n* 867)		Controls (*n* 824)		
Variables	Mean	SD	Mean	SD	*P*
Age (years)	47·2	9·7	46·9	10·1	0·43
BMI (kg/m^2)	23·1	3·3	22·6	3·1	<0·01
Age at menarche (years)	14·5	1·9	14·6	1·7	0·22
Age at first live birth (years)*	25·7	3·7	25·5	3·2	0·33
DII score	−1·8	1·7	−1·2	1·9	<0·01
	n	%	*n*	%	
Marital status					0·64
Married	819	94·5	774	93·9	
Unmarried/divorced/widowed	48	5·5	50	6·1	
Education level					<0·01
Primary school or below	218	25·1	218	26·5	
Junior high school	260	30·0	188	22·8	
Senior high school/secondary technical school	318	36·7	293	35·6	
College or above	71	8·2	125	15·2	
Occupation					0·36
Blue collar worker	249	28·7	220	26·7	
Administrator/other white collar worker	164	18·9	177	21·5	
Farmer/other	454	52·4	427	51·8	
Income level (yuan/month)					<0·01
<2000	125	14·4	49	5·9	
2001–5000	258	29·8	186	22·6	
5001–8000	281	32·4	303	36·8	
>8001	203	23·4	286	34·7	
Physical activity (exercise for health)					0·44
Never	375	43·3	319	38·7	
Seldom	59	6·8	35	4·2	
Often	433	49·9	470	57·0	
Regular smoker	14	1·6	12	1·5	0·71
Passive smoking	563	64·9	428	51·9	<0·01
Regular drinker	68	7·8	52	6·3	0·22
Menopausal status					0·99
Premenopausal	561	64·7	533	64·7	
Postmenopausal	306	35·3	291	35·3	
Breast-feeding history†	728	84·0	683	82·9	0·84
Parity					0·19
0	39	4·5	39	4·7	
1–2	637	73·5	633	76·8	
≥3	191	22·0	152	18·4	
First-degree relative with cancer	127	14·6	75	9·1	<0·01
History of benign breast disease	307	35·4	205	24·9	<0·01
Ever used an oral contraceptive	65	7·5	45	5·5	0·09
Hormone replacement therapy use	31	3·6	26	3·2	0·63
Hormonal receptor status‡					
ER+ and PR+	417	48·1			
ER+ or PR+ (but not both)	71	8·2			
ER− and PR−	194	22·4			

DII, Dietary Inflammatory Index; ER, oestrogen receptor; PR, progesterone receptor.
* Among women who had a live birth.
† Among breast-feeding women.
‡ Among cases.

increasing levels of the DII. The crude OR was 2·08 (95 % CI 1·59, 2·73) comparing the highest with the lowest quartile ($P_{trend} < 0·001$). After adjusting for potential confounding factors, the association remained significant, with an adjusted OR for the highest quartile compared with the lowest of 2·28 (95 % CI 1·71, 3·03) ($P_{trend} < 0·001$).

The results of stratified analyses also are shown in Table 3. Totally, there were 1094 premenopausal women (561 cases and 533 controls) and 597 postmenopausal women (306 controls and 291 cases). A proinflammatory diet was found to increase the risk of breast cancer in both premenopausal and postmenopausal women (highest *v.* lowest quartile: adjusted OR 2·60 among premenopausal women; 95 % CI 1·81, 3·78, $P_{trend} < 0·001$; adjusted OR 1·89 among postmenopausal women; 95 % CI 1·17, 3·06, $P_{trend} = 0·005$).

When cases were stratified based on ER and PR status, 414 cases were in ER+ and PR+ stratum, seventy-one cases in ER+ or PR+ stratum and 194 cases in ER− and PR− status.

Table 2. Nutrition data across quartiles (Q) of the Dietary Inflammatory Index score in a Chinese case–control study, 2011–2016 (Medians and 25th, 75th percentiles)

Variables	Overall inflammatory effect score	Q1		Q2		Q3		Q4		*P*
		Median	P25, P75	Median	P25, P75	Median	P25, P75	Median	P25, P75	
Vitamin B_{12} (mg/d)	0·106	2	1, 2	2	1, 3	2	1, 2	2	1, 3	0·46
Vitamin B_6 (mg/d)	−0·365	1	1, 1	1	1, 1	1	1, 1	1	1, 1	0·84
β-Carotene (mg/d)	−0·584	3650	2663, 4800	3736	2842, 4754	3615	2619, 4607	3381	2500, 4754	0·09
Carbohydrate (g/d)	0·097	213	182, 256	218	186, 261	213	187, 254	215	187, 261	0·68
Cholesterol (mg/d)	0·11	304	227, 407	311	211, 417	285	204, 376	292	201, 417	0·04
Total fat (g/d)	0·298	57	43, 75	57	42, 72	52	42, 68	57	44, 72	0·04
Fibre (g/d)	−0·663	9	7, 11	9	7, 10	8	7, 11	9	7, 10	0·61
Folic acid (μg/d)	−0·19	206	170, 256	209	175, 250	198	165, 240	203	165, 250	0·04
Garlic (g/d)	−0·412	0	0, 2	0	0, 2	1	0, 2	1	0, 2	0·67
Fe (mg/d)	0·032	17	15, 20	17	15, 20	17	14, 20	16	14, 20	0·04
Mg (mg/d)	−0·484	248	210, 292	245	207, 289	240	199, 281	239	200, 289	0·1
MUFA (g/d)	−0·009	21	16, 28	20	16, 28	20	16, 28	23	17, 28	<0·01
Niacin (mg/d)	−0·246	15	12, 18	15	12, 18	14	12, 17	14	12, 18	0·08
n-3 Fatty acids (g/d)	−0·436	1	1, 1	1	1, 2	1	1, 1	1	1, 2	0·16
n-6 Fatty acids (g/d)	−0·159	12	9, 17	12	9, 16	12	9, 17	13	10, 16	0·02
Onion (g/d)	−0·49	1	0, 5	1	0, 5	1	0, 5	1	0, 5	0·68
Protein (g/d)	0·021	64	53, 76	64	54, 75	62	50, 74	62	52, 75	0·17
PUFA (g/d)	−0·337	12	9, 17	12	9, 17	12	9, 17	13	10, 17	0·01
Riboflavin (mg/d)	−0·068	1	1, 1	1	1, 1	1	1, 1	1	1, 1	0·73
SFA (g/d)	0·373	13	10, 17	13	10, 17	12	10, 18	14	10, 17	0·01
Se (mg/d)	−0·191	41	32, 56	42	31, 56	39	31, 51	41	30, 56	0·15
Thiamin (mg/d)	−0·098	1	1, 1	1	1, 1	1	1, 1	1	1, 1	0·21
Vitamin A (RE/d)	−0·401	791	590, 1037	798	603, 1014	766	560, 965	727	546, 1014	0·02
Vitamin C (mg/d)	−0·424	143	99, 191	149	114, 183	143	102, 180	134	100, 183	0·06
Vitamin E (mg/d)	−0·419	10	8, 13	10	8, 13	10	8, 12	10	8, 13	0·23
Zn (mg/d)	−0·313	8	7, 9	8	7, 10	8	6, 9	8	7, 10	0·48
Flavan-3-ol (mg/d)	−0·415	6	3, 10	6	3, 11	6	4, 10	6	3, 11	0·65
Flavones (mg/d)	−0·616	5	3, 9	6	3, 9	5	3, 8	6	3, 9	0·44
Flavonols (mg/d)	−0·467	27	19, 38	28	21, 37	27	19, 36	26	18, 37	0·08
Flavonones (mg/d)	−0·25	3	2, 5	3	2, 5	3	2, 5	3	2, 5	0·45
Anthocyanidins (mg/d)	−0·131	16	10, 25	16	11, 25	16	10, 25	17	10, 25	0·74
Isoflavones (mg/d)	−0·593	7	3, 12	7	3, 11	5	3, 10	6	2, 11	0·08
Pepper (g/d)	−0·397	0	0, 4	0	0, 5	0	0, 5	0	0, 5	0·52

Compared with the lowest quartile, both the 3rd and 4th quartiles of the DII score were positively associated with ER+ and PR+ breast cancer (adjusted OR 1·76; 95 % CI 1·20, 2·56; adjusted OR 2·81; 95 % CI 1·96, 4·03; $P_{trend} < 0·001$). Among women with ER+ or PR+ status (but not both), the OR comparing the highest quartile with the lowest quartile was not significant. We also observed a positive association of breast cancer with DII scores in the ER− and PR− subtype (adjusted OR 2·13; 95 % CI 1·35, 3·49; $P_{trend} < 0·001$).

In this study, 110 women (forty-eight cases and sixty-two controls) were underweight, 1047 (531 cases and 516 controls) were within normal weight, 427 (223 cases and 204 controls) were overweight and 107 (sixty-five cases and forty-two controls) were obese. Positive associations between DII score and breast cancer were found among normal weight, overweight and obese women (highest *v.* lowest quartile: adjusted OR 1·97 among normal weight women; 95 % CI 1·37, 2·81, $P_{trend} < 0·001$; adjusted OR 2·60 among overweight women; 95 % CI 1·47, 4·57, $P_{trend} = 0·001$; adjusted OR 4·96 among obese women; 95 % CI 1·35, 18·23, $P_{trend} = 0·008$), but no association was found among underweight women.

The correlation coefficients between each of the food parameters comprising the DII were calculated. The results showed that several components of DII were correlated with each other (online Supplementary Table S3). Some food parameters were strongly correlated, such as *β*-carotene and vitamin C (correlation coefficient = 0·89). Some were weakly correlated such as garlic and thiamin (correlation coefficient = 0·01).

Discussion

In this case–control study, a positive association was found between a higher DII score (corresponding to a proinflammatory diet) and breast cancer risk among Chinese women. We also observed that higher DII scores were related to increased risk of breast cancer among women with ER+ and PR+ status and ER− and PR− status but not women with either ER+ or PR+ status (but not both). When stratified by BMI, positive associations between DII and breast cancer were observed among normal weight, overweight and obese women but not among underweight women. In addition, the results of stratification analyses indicated that the inflammatory effect of diet on breast cancer was independent of menopausal status.

Chronic inflammation is a key contributor in the development and progression of carcinogenesis[6]. Inflammatory pathways play an important role in the causation of breast cancer[40]. Some risk factors for breast cancer (age, obesity, menopause and diet) are associated with systemic inflammation, as indicated by increased

Table 3. Dietary Inflammatory Index (DII) score and breast cancer risk in a Chinese case–control study, 2011–2016
(Mean values and standard deviations; odds ratios and 95 % confidence intervals)

	Q1		Q2		Q3		Q4			Continuous		
Variables	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}*	OR	95 % CI	*P*
Overall												
Cases/controls (*n*)	162/205		159/207		210/208		336/204			867/824		
DII score												
Mean	−3·58		−2·45		−1·50		0·61			−1·48		
SD	0·61		0·20		0·32		1·24			1·78		
Crude OR	1	0·97	0·73, 1·30	1·28	0·96, 1·69	2·08	1·59, 2·73	<0·001	1·36	1·23, 1·51	<0·001	
Adjusted OR†	1	1·01	0·75, 1·38	1·42	1·05, 1·91	2·28	1·71, 3·03	<0·001	1·40	1·25, 1·39	<0·001	
Menopausal status												
Premenopausal												
Cases/controls (*n*)	103/135		103/138		143/133		212/127			561/533		
DII score												
Mean	−3·60		−2·45		−1·50		0·59			−1·52		
SD	0·62		0·25		0·32		1·21			1·76		
Crude OR	1	0·98	0·68, 1·40	1·41	0·99, 2·00	2·19	1·56, 3·07	<0·001	1·39	1·22, 1·59	<0·001	
Adjusted OR†	1	0·95	0·64, 1·41	1·59	1·08, 2·31	2·60	1·81, 3·78	<0·001	1·50	1·30, 1·73	<0·001	
Postmenopausal												
Cases/controls (*n*)	59/70		56/69		67/75		124/77			306/291		
DII score												
Mean	−3·55		−2·44		−1·50		0·66			−1·42		
SD	0·57		0·25		0·32		1·30			1·83		
Crude OR	1	0·96	0·59, 1·58	1·06	0·66, 1·71	1·91	1·22, 2·99	0·002	1·28	1·15, 1·41	0·002	
Adjusted OR†	1	1·09	0·64, 1·83	1·23	0·74, 2·06	1·89	1·17, 3·06	0·005	1·27	1·06, 1·53	0·01	
Sex hormone status												
ER+ and PR+												
Cases/controls (*n*)	66/205		74/207		108/208		169/204			417/824		
DII score												
Mean	−3·56		−2·45		−1·52		0·64			−1·53		
SD	0·59		0·25		0·32		1·24			1·76		
Crude OR	1	1·11	0·76, 1·63	1·61	1·12, 2·32	2·57	1·82, 3·63	<0·001	1·48	1·30, 1·68	<0·001	
Adjusted OR†	1	1·17	0·79, 1·75	1·76	1·20, 2·56	2·81	1·96, 4·03	<0·001	1·50	1·31, 1·72	<0·001	
ER+ or PR+												
Cases/controls (*n*)	16/205		10/207		17/208		28/204			71/824		
DII score												
Mean	−3·55		−2·45		−1·54		0·55			−1·71		
SD	0·58		0·25		0·32		1·23			1·68		
Crude OR	1	0·62	0·27, 1·40	1·05	0·52, 2·13	1·76	0·92, 3·35	0·030	1·36	1·05, 1·76	0·02	
Adjusted OR†	1	0·62	0·26, 1·44	1·09	0·52, 2·30	1·91	0·97, 3·80	0·022	1·41	1·07, 1·86	0·015	
ER− and PR−												
Cases/controls (*n*)	41/205		36/207		36/208		81/204			194/824		
DII score												
Mean	−3·56		−2·45		−1·51		0·56			−1·65		
SD	0·60		0·25		0·32		1·29			1·73		
Crude OR	1	0·87	0·53, 1·42	0·87	0·53, 1·41	1·99	1·30, 3·03	0·001	1·36	1·15, 1·60	<0·001	
Adjusted OR†	1	0·93	0·56, 1·55	0·91	0·54, 1·52	2·13	1·35, 3·49	0·001	1·35	1·14, 1·61	0·001	
BMI (kg/m^2)												
Underweight (<18·5)												
Cases/controls (*n*)	7/14		7/12		14/19		20/17			48/62		
DII score												
Mean	−3·5		−2·43		−1·55		0·26			−1·52		
SD	0·51		0·26		0·3		1·19			1·76		
Crude OR	1	1·17	0·32, 4·28	1·47	0·47, 4·61	2·35	0·77, 7·17	0·103	1·52	0·96, 2·42	0·08	
Adjusted OR†	1	1·32	0·27, 6·45	1·39	0·33, 5·91	3·80	0·93, 15·63	0·060	1·76	0·99, 3·13	0·06	
Normal weight (≥18·5 and <24)												
Cases/controls (*n*)	107/121		94/135		120/130		210/130			531/516		
DII score												
Mean	−3·61		−2·45		−1·51		0·67			−1·47		
SD	0·64		0·24		0·33		1·22			1·82		
Crude OR	1	0·79	0·54, 1·14	1·04	0·73, 1·50	1·83	1·30, 2·57	<0·001	1·32	1·16, 1·50	<0·001	
Adjusted OR†	1	0·84	0·57, 1·24	1·20	0·82, 1·75	1·97	1·37, 2·81	<0·001	1·34	1·17, 1·53	<0·001	

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Table 3. *Continued*

Variables	Q1		Q2		Q3		Q4			Continuous		
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}*	OR	95 % CI	*P*
Overweight (≥24 and <28)												
Cases/controls (*n*)	40/57		46/48		58/54		79/45			223/204		
DII score												
Mean	−3·48		−2·45		−1·48		0·48			−1·58		
SD	0·52		0·25		0·31		1·19			1·65		
Crude OR	1		1·37	0·77, 2·42	1·53	0·88, 2·65	2·50	1·45, 4·32	<0·001	1·41	1·12, 1·76	0·003
Adjusted OR†	1		1·44	0·80, 2·61	1·48	0·84, 2·61	2·60	1·47, 4·57	0·001	1·41	1·12, 1·77	0·004
Obese (≥28)												
Cases/controls (*n*)	8/13		12/12		18/5		27/12			65/42		
DII score												
Mean	−3·82		−2·45		−1·47		0·86			−1·30		
SD	0·63		0·27		0·33		1·58			2·07		
Crude OR	1		1·63	0·49, 5·34	5·85	1·55, 22·02	3·66	1·20, 11·12	0·009	1·60	1·06, 2·42	0·02603
Adjusted OR†	1		1·71	0·44, 6·61	6·68	1·51, 30·83	4·96	1·35, 18·23	0·008	1·77	1·09, 2·88	0·021

Q, quartiles; ER, oestrogen receptor; PR, progesterone receptor.
* P_{trend} for linear trend.
† Adjusted for education, income, passive smoking, BMI, first-degree relative with cancer and history of benign breast disease.

levels of circulating proinflammatory cytokines[41–45]. Effects of diet and dietary components on inflammation have been identified[4,46–48]. However, little evidence exists on the proinflammatory and anti-inflammatory effects of the overall diet on breast cancer risk. The DII was developed and refined to quantify the inflammatory potential of individual diets based on the literature that assessed each food parameter having a positive or negative effect on inflammation[19]. For example, consistent with prior research linking SFA intake to increased inflammation[4], the overall inflammatory score for SFA used in the DII calculation process is 0·373. This high score represents a strong proinflammatory effect. The DII has been used to evaluate the inflammatory effects of diet on the incidence of various diseases, including CVD, the metabolic syndrome and various cancers[20–32,49–51].

To date, there have been two case–control studies and four prospective studies investigating the inflammatory effects of diet on breast cancer risk[27–32]. Consistent with the findings of the current study, one case–control and two prospective studies produced results consistent with a proinflammatory diet increasing the risk of breast cancer[28–30]. However, a recent study based on data from the Women's Health Initiative, the DII was not associated with incidence of overall breast cancer; though increasing DII score was associated with a higher risk of death from breast cancer[31]. Consistent with this null result, no association was observed in a case–control study conducted in Germany among postmenopausal women[27]. Also the analysis based on the Women's Health Initiative found that a history of proinflammatory diets or sustained intake of highly proinflammatory diets may be associated with a higher risk of developing the ER−, PR−, HER2+ subtype of breast cancer[32].

Results from previous studies on the association between the DII score and breast cancer based on menopausal status have been mixed. A previous prospective study conducted in Sweden found that a higher DII score increased the risk of breast cancer, most convincingly among postmenopausal women[30]. Another recent prospective study using data from the Iowa Women's Health Study also observed that a proinflammatory diet appears to increase the risk of developing breast cancer in postmenopausal women[28]. However, no significant association was observed among postmenopausal women in the German case–control study[27]. In the present study, the DII score was positively associated with breast cancer risk in both premenopausal and postmenopausal women.

We found that a higher DII score was associated with greater breast cancer in women with both hormone receptor (ER and PR)-positive or hormone receptor-negative status, but not significantly in women with just ER+ or PR+ alone. A key downstream mediator of proinflammatory cytokines is the NF-κB family of transcription factors, which is known to play a critical role in the development and progression of a variety of tumours[52]. Previous studies have found NF-κB activation to be predominantly associated with ER− breast tumours[53]. However, there is an increasing amount of evidence that NF-κB activation occurs in ER+ tumours[54]. The cause of NF-κB activation is largely unknown, but the status of PR, which has been shown to have an anti-inflammatory role in breast cancer cells, may be one contributing factor[55]. Thus, we speculate that

there is different dietary inflammatory effect on the risk of breast cancer subtypes according to different hormone receptor status. This is an area requiring more intensive research.

Compared with the association among women within normal weight, a stronger positive association between the DII score and breast cancer was observed among overweight and obese women in the present study; however, no significant association was found for underweight women. This finding is consistent with the idea that overweight or obese women are more sensitive to the effects of inflammatory stimuli[41]. One likely explanation for the tight link between obesity, inflammation and breast cancer can be explained by the recruitment of macrophages into adipose tissue, where they form characteristic 'crown-like' structures around apoptotic adipocytes. Macrophages and adipocytes are able to produce inflammatory factors, such as adipokines and cytokines, leading to activation of the proinflammatory transcription factor NF-κB in adipose tissue and liver[54]. The other reasonable explanation may be the observation that adipocytes express aromatase and that this enzyme is up-regulated in the adipose tissue of obese women resulting in elevated sex-hormones biosynthesis. Aromatase expression is regulated not only by PG but also by proinflammatory cytokines[56]. However, underweight women had less adipose tissue and the less apoptotic adipocytes and aromatase expression. The inflammatory effect of diet may be too weak to make a difference in the development of breast cancer for underweight women who are less sensitive to the effects of inflammation[41].

The strengths of this study are the relatively large sample, the satisfactory reproducibility and the reasonable validity of the 81-item FFQ[57]. In addition, to the best of our knowledge, this is the first study to investigate the association of inflammatory effects of diet with breast cancer by the DII in China. Despite its strengths, some limitations should be acknowledged. First, although most of the forty-five DII variables were taken into account (n 33), some items (n 12) were not available for the DII calculation, such as alcohol, caffeine, eugenol, saffron, green tea, vitamin D ginger, turmeric, thyme or oregano, rosemary (anti-inflammatory factors) and *trans*-fat acids (proinflammatory factor) that were usually consumed in small amounts, infrequently, or not consumed at all in the Chinese women; thus, they may not have had a major impact on the scoring. Second, selection bias and recall bias are inevitable in hospital-based case–control studies. To minimise selection bias, all control subjects were carefully recruited to exclude any diagnosis potentially related either to breast cancer or dietary changes. The time-concordant period of hospitalisation and identical catchment areas of all subjects, and the relatively high response rate also helped to reduce selection bias. In addition, to minimise recall bias, cases were interviewed as soon as the diagnosis was made. In addition, in the present study, greater effort was invested in interviewing cases before their surgery. Moreover, food photographs were provided to assist participants with quantification of dietary intake. Third, in the present study, the controls were recruited from the hospitals. The participant referrals had a higher proportion of more highly educated women than that of the general population[58]. As such, the participants might have different dietary habits; and maybe have been able to provide more accurate responses to questionnaires. Therefore, generalising the findings in this study should be made with caution. Fourth, there also were potential confounders that we were unable to measure, and therefore, residual confounding might also remain even though various dietary and non-dietary confounders were adjusted. However, potential confounding bias may be minimised by adjusting for a wide range of known confounding factors, such as income, BMI, family history of breast cancer and history of benign breast disease. Fifth, because CRP or other inflammation parameters in blood levels were not measured in the present study, we cannot evaluate how much of the variation of inflammatory markers could be explained by the DII. Further studies are needed to clarify this association. Sixth, we did observe collinearity between intake values of various food parameters which is integral to any dietary pattern and diet score.

In conclusion, compared with women who consumed an anti-inflammatory diet, women who consumed a more proinflammatory diet appeared to be at increased risk of breast cancer, especially overweight and obese women (i.e. with BMI >24 kg/m^2) and women with ER+ and PR+ status and ER− and PR− status. Further studies are needed to investigate the mutual relationships between the inflammatory effect of diet, circulation cytokines levels and the risk of developing breast cancer.

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The authors' responsibilities were as follows: W.-Q. H. collected the data, analysed the data and wrote the paper; X.-F. M., Y.-B. Y. and F.-Y. L. were responsible for connecting and coordinating the field work; N. S. computed the DII and contributed to the revision of the manuscript; J. R. H. and B. Y. participated in data collection; J. R. H. invented the DII and helped in the revision of the manuscript; C.-X. Z. constructed the project design, supervised the study and contributed to manuscript writing.

J. R. H. owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the DII from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. N. S. is an employee of CHI. The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114517001192

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