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Prospective study of dietary inflammatory index and risk of breast cancer in Swedish women

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Background: The role of diet in breast cancer (BrCa) aetiology has been studied widely. Although the results are inconsistent, dietary components have been implicated through their effects on inflammation. We examined the association between a dietary inflammatory index (DII) and BrCa incidence in the Swedish Women's Lifestyle Study.

Methods: The DII was computed at baseline from a validated 80-item food frequency questionnaire in a cohort of 49 258 women, among whom 1895 incident BrCa cases were identified through linkage with the National Cancer Registry through 2011. We used multivariable Cox proportional models to estimate hazard ratios (HR).

Results: Positive associations were observed between DII and BrCa (HR_{DII quartile 4 vs 1} = 1.18; 95% CI: 1.00, 1.39), with somewhat stronger associations in postmenopausal women (HR_{DII quartile 4 vs 1} = 1.22; 95% CI: 1.01, 1.46).

Conclusions: A proinflammatory diet appears to increase the risk of developing BrCa, especially in postmenopausal women.

Breast cancer (BrCa) is the most common cancer in Swedish women, representing 30.3% of all cancer cases in 2011. Beyond reproductive and hormonal factors (Faupel-Badger *et al*, 2013) and a few strongly penetrant genes (Dumitrescu and Cotarla, 2005), not much is known with certainty about the causes of BrCa. However, evidence suggests a role for the ability of diet to modulate inflammation in the aetiology of the disease (American Institute for Cancer Research, 2007).

Inflammation is a result of the body's response to tissue insult/injury or to inflammatory stimulants (Keibel *et al*, 2009; Pan *et al*, 2009). Chronic inflammation is a known risk factor for several cancers (Philip *et al*, 2004; Baniyash *et al*, 2014). Research on the possible effects of diet, inflammation, and cancer occurrence is, however, methodologically challenging (Hebert and Miller, 1988). However, the newly developed dietary inflammatory index (DII) (Shivappa *et al*, 2014b) has been shown to predict the levels of inflammatory markers

(Shivappa *et al*, 2014c, 2015b) and cancer outcomes (Shivappa *et al*, 2015a; 2014a) in diverse populations.

Specific dietary components may influence both inflammation (Galland, 2010) and BrCa risk (Linos and Willett, 2007). Inflammatory cytokines and other factors that regulate inflammation might be associated with BrCa (Harris *et al*, 2014) and might modify the effect of hormonal factors that are causally related to BrCa (Touvier *et al*, 2013). We therefore examined the association between the DII and BrCa incidence in the Swedish Women's Lifestyle Health (SWLH) study. Our hypothesis is that a higher DII score (indicating proinflammatory diet) increases the risk of incident BrCa.

SUBJECTS AND METHODS

Study cohort. Details regarding the SWLH cohort design have been published elsewhere (Kumle *et al*, 2002). In brief, the cohort

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consisted of 49 258 women who returned a completed comprehensive questionnaire in 1991–1992. Incident breast cancers were obtained through linkage with the National Cancer Register. The SWLH study was approved by the Swedish Data Inspection Board and the Regional Ethical Committee of Uppsala University and Karolinska Institutet. All participants signed an informed consent form.

Dietary inflammatory index. Dietary data were collected using a validated 80-item food frequency questionnaire (FFQ) completed at baseline. Nutrients were determined using the Swedish National Food Administration database. Developing the DII involved reviewing and scoring nearly 2000 scientific articles representing

studies of different design on diet and inflammation. To calculate the DII, dietary data were first linked to the previously described regionally representative world database that provided a mean and standard deviation for each parameter (Shivappa *et al*, 2014b). These then became the multipliers to express an individual's exposure relative to the 'standard global mean' (from the 11 data sets used for comparative purposes) as a z-score. We converted this score to a centred percentile score, which was then multiplied by the respective food parameter effect score, to obtain a food parameter-specific DII score (Shivappa *et al*, 2014b). All of the food parameter-specific DII scores were then summed to create the overall DII score for every participant. The methodology is depicted in Figure 1. For the current study, data on 29 of the 45

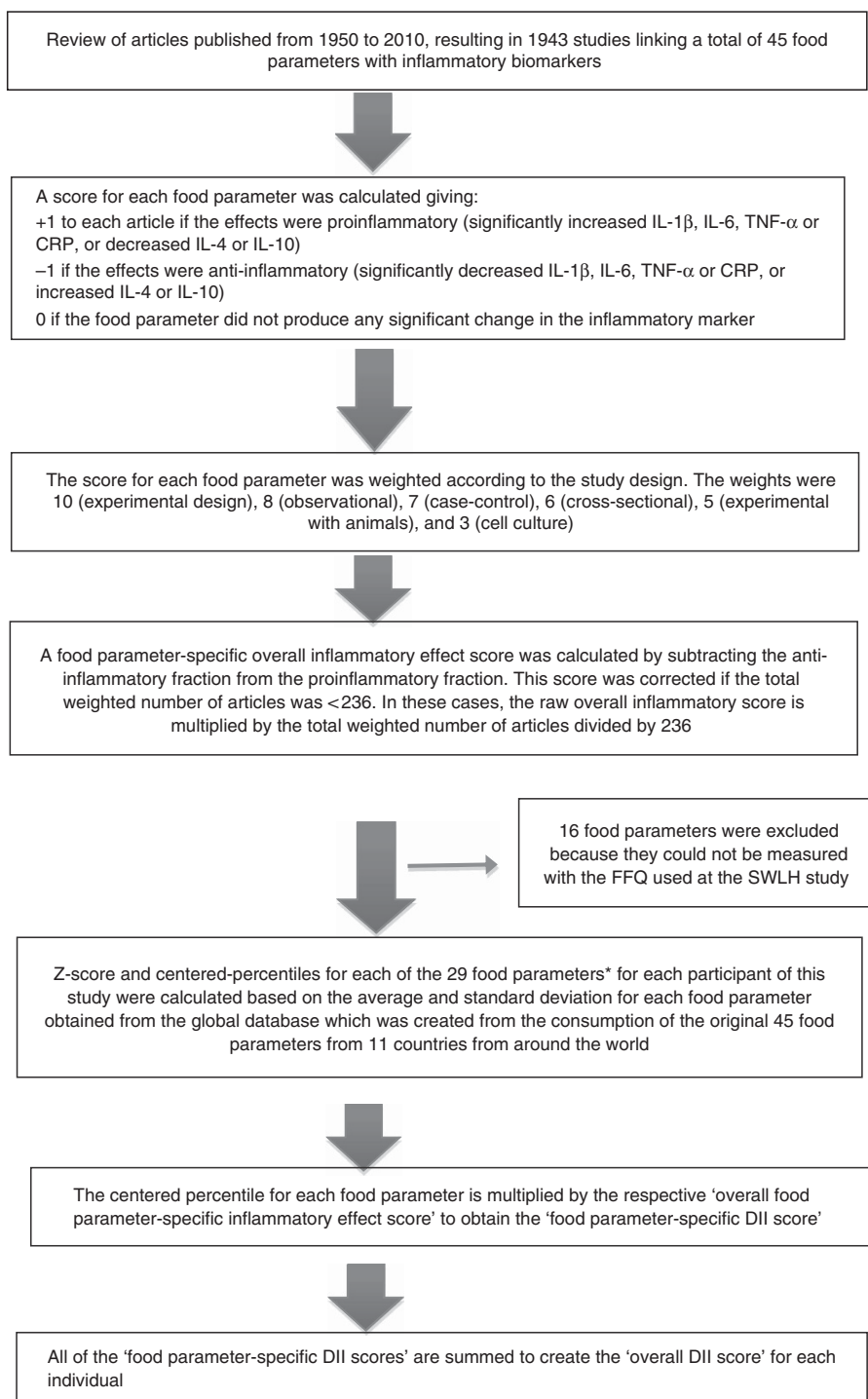


Figure 1. Sequence of steps in creating the dietary inflammatory index in the SWLH study.

possible food parameters were available for DII calculation (Supplementary Table 1).

Follow-up. The cohort was followed from 1992 until 31 December 2012. Follow-up time was calculated from the date of entry into the cohort until the occurrence of BrCa, emigration, death, or the end of the observation period, whichever came first. A total of 1895 newly diagnosed incident BrCa cases were identified (International Classification of Diseases, 7th revision, code 170.0).

We determined age at menopause by combining information from the baseline questionnaire with a follow-up questionnaire conducted in 2002–2003, with responses obtained from 29 867 participants. Women without information on age at menopause were considered postmenopausal at 53 years of age (i.e., the 75th percentile of age at menopause in the study population).

Statistical analyses. Participants were excluded if they had been diagnosed with BrCa at or before recruitment ($N=244$), or had extreme energy intake outside the 1st and 99th percentiles ($N=981$). Study characteristics were examined across DII quartiles (Table 1).

Dietary inflammatory index was analysed both as a continuous variable and as quartiles. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models, adjusting only for age in Model 1. Model 2

additionally adjusted for history of BrCa in a first-degree relative, smoking, BMI, height, age at first birth, total number of children, educational level (years in school), age at menarche, total energy intake, multivitamin use, and oral contraceptive use. The covariates were chosen *a priori*, as they are established or suggested as risk factors for BrCa. A linear test for trend was conducted using the median approach. The assumption of proportional hazards was tested by adding to the model an interaction term between follow-up time and DII; there was no evidence that these assumptions were violated.

Nearly significant interaction was observed for menopausal status (P -value = 0.06); hence, the analyses also were stratified by menopausal status. To account for the possibility that a change in dietary pattern occurred since baseline, sensitivity analysis was performed restricting the follow-up to 10 years (1991–2001). Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA); all tests of statistical hypothesis were made on the two-sided 5% level of significance.

RESULTS

Data from 45 257 women were available, with an average follow-up period of 20 years. Mean DII was 2.67 (s.d. = ± 1.47). Across

Table 1. Prevalence of characteristics at baseline across quartiles of DII in the SWLH study

Characteristics ^b (mean (s.d.) or %)	DII ^a			
	Quartile 1 <1.87 Median = 1.01 N = 11 314	Quartile 2 1.87–2.92 Median = 2.45 N = 11 315	Quartile 3 2.93–3.77 Median = 3.36 N = 11 313	Quartile 4 >3.77 Median = 4.24 N = 11 315
Breast cancer cases (%)	454 (4.0)	493 (4.4)	468 (4.1)	480 (4.2)
Stage of breast cancer				
<i>In situ</i>	64 (14.4)	69 (15.1)	69 (16.1)	66 (14.0)
Invasive	390 (85.6)	424 (84.9)	399 (83.9)	414 (85.0)
Age (years)	40.4 (5.7)	40.3 (5.7)	40.2 (5.7)	40.3 (5.8)
Age at menarche (years)	12.9 (1.4)	12.9 (1.3)	13.0 (1.3)	13.0 (1.3)
Total energy intake (kcal per day)	1924 (409)	1655 (356)	1462 (332)	1193 (344)
PUFA (g per day)	9.6 (3.1)	8.1 (2.4)	7.1(2.1)	5.7 (2.0)
Dietary fibre (g per day)	19.6 (4.5)	15.0 (2.9)	12.4 (2.6)	9.4 (2.7)
BMI (kg m ⁻²)	23.6 (3.7)	23.5 (3.7)	23.4 (3.6)	23.4 (3.7)
Education (%)				
Low	37.4	41.4	45.9	53.0
High	62.6	58.6	54.1	47.0
Smoking (%)				
Never	47.5	43.2	39.6	34.2
Former	36.9	37.4	38.1	37.4
Current	15.6	19.4	22.3	28.4
Multivitamin use (%)	18.3	16.0	14.0	11.0
Oral contraceptive use (yes) (%)	60.4	61.0	60.9	59.3
Age at first birth (years) and total number of children at baseline				
Parity				
No children	9.1	8.9	9.7	11.3
<30, 1 child	4.4	4.9	5.2	6.3
<30, 2 children	25.9	28.1	29.5	26.8
<30, ≥ 3 children	26.4	24.8	23.0	21.6
≥ 30 , 1 child	7.9	7.5	8.2	9.2
≥ 30 , 2 children	17.2	17.4	16.4	16.5
≥ 30 , ≥ 3 children	9.1	8.3	8.2	8.4
Physical activity (%)				
Sitting only/sedentary	2.8	3.2	4.2	6.6
Walking only	65.8	69.8	72.3	73.1
Moderate	20.2	18.3	15.5	13.9
Vigorous	11.2	8.7	7.9	6.4

Abbreviations: DII = dietary inflammatory index; N = number of women; PUFA = polyunsaturated fatty acid; SWLH = The Swedish cohort Women Lifestyle and Health.

^aQuartile 1 refers to scores indicating anti-inflammatory diet and quartile 4 refers to scores indicating a proinflammatory diet.

^bAll variables are at baseline. Some column percentages are presented; they do not always add to 100 because of rounding.

Table 2. DII and breast cancer risk by menopausal status

	Quartile 1 <1.87 Median = 1.01 N = 11 314	Quartile 2 1.87–2.92 Median = 2.45 N = 11 315	Quartile 3 2.93–3.77 Median = 3.36 N = 11 313	Quartile 4 >3.77 Median = 4.24 N = 11 315	P-value ^a	DII continuous
Cases/person years	454/203 583	493/204 109	468/203 472	480/203 050		1895/81 4214
Overall						
Model 1 ^b (HR, 95% CI)	1 ^a	1.09 (0.96, 1.24)	1.05 (0.93, 1.20)	1.08 (0.95, 1.22)	0.32	1.02 (0.98, 1.01)
Model 2 ^c (HR, 95% CI)	1 ^a	1.11 (0.97, 1.23)	1.10 (0.95, 1.23)	1.18 (1.00, 1.39)	0.07	1.04 (1.01, 1.09)
Menopausal status						
Pre						
Model 1 ^b (HR, 95% CI)	1 ^a	0.92 (0.69, 1.22)	0.77 (0.56, 1.05)	0.96 (0.68, 1.34)	0.45	0.94 (0.86, 1.02)
Model 2 ^c (HR, 95% CI)	1 ^a	0.93 (0.70, 1.24)	0.76 (0.55, 1.04)	0.96 (0.68, 1.35)	0.43	0.93 (0.86, 1.02)
Post						
Model 1 ^b (HR, 95% CI)	1 ^a	1.17 (1.00, 1.37)	1.20 (1.02, 1.41)	1.22 (1.02, 1.47)	0.02	1.07, 1.02, 1.12
Model 2 ^c (HR, 95% CI)	1 ^a	1.17 (1.00, 1.36)	1.18 (1.00, 1.40)	1.22 (1.02, 1.46)	0.03	1.07, 1.02, 1.12

Abbreviations: BMI = body mass index; CI = confidence interval; DII = dietary inflammatory index; HR = hazard ratio.
^aP-value for trend determined through the median approach.
^bModel 1: Age-adjusted.
^cModel 2: Adjusted for energy, age at first birth and number of children, age at menarche, BMI, height, multivitamin use, education, smoking status, oral contraceptive use, and family history of breast cancer in the model.

increasing DII quartiles, decreasing trends were observed for energy, PUFA, and dietary fibre intake, multivitamin use, higher education, and oral contraceptive use. Increasing trends were observed for current smokers, nulliparous women, and those reporting low levels of physical activity (Table 1).

Multivariable analyses showed positive associations with BrCa risk both when DII was analysed as a continuous variable (HR = 1.04; 95% CI: 1.00–1.09) and in quartiles (HR_{DII quartile 4 vs 1} = 1.18; 95% CI: 1.00–1.39, *P*-value for trend = 0.07) (Table 2). When analyses were stratified by menopausal status, DII was associated with breast cancer only among postmenopausal women (HR_{DII quartile 4 vs 1} = 1.22; 95% CI: 1.01, 1.46). Sensitivity analysis carried out by restricting the follow-up to 10 years showed similar results (HR_{continuous} = 1.08; 95% CI: 1.01–1.16) (Table 2).

DISCUSSION

Our prospective study of Swedish women showed evidence of a positive association between a proinflammatory diet and incident BrCa, most convincingly among postmenopausal women. Previous studies on diet and BrCa have shown mixed results. Mediterranean diet and diets composed largely of vegetables, fruit, fish, and soy are associated with a decreased risk (Albuquerque *et al*, 2014). However, previously the SWLH showed no association with Mediterranean dietary pattern (Couto *et al*, 2013). This should not be too surprising as a healthy Swedish diet may not adhere to the Mediterranean prescription. In a large European cohort (the EPIC study), saturated fat showed only a marginal association with BrCa risk (Sieri *et al*, 2008), whereas other studies have found no association (Willett and Hunter, 1994; Park *et al*, 2012).

Consistent with the results from other studies on diet and BrCa (Linos and Willett, 2007), we observed a stronger association among postmenopausal women. In the EPIC study, adherence to a Mediterranean score was associated with a modest reduction in the risk of BrCa in postmenopausal women with no association among premenopausal women (Buckland *et al*, 2013). In other studies, higher CRP and IL-1 β levels increased the risk of developing BrCa (Onitilo *et al*, 2012; Pooja *et al*, 2012). The DII has previously been shown to be positively associated with these cytokines (Shivappa *et al*, 2014c, 2015b). A positive association of the DII with BrCa might arise through the effect of proinflammatory diet on

increasing systemic inflammation through activation of insulin-like growth factor receptor (Festa *et al*, 2000; Esmailzadeh *et al*, 2007).

Strengths of the present study include its population-based design, large sample size, prospective data collection with extended follow-up and near-complete case ascertainment. One limitation is that DII was calculated just once with an instrument that is prone to measurement error. However, no disease-related information bias was possible because of the prospective study design and adult dietary patterns appear to remain relatively stable over time (Jensen *et al*, 1984; Jain *et al*, 1989). Also, a change in dietary pattern since baseline would be expected to dilute an effect of diet. Therefore, the fact that results did not vary much in the sensitivity analysis where we restricted our data to only 10 years of follow-up is *prima facie* evidence of lack of a biasing effect of time since FFQ data were collected.

Another limitation could be the non-availability of 16 food parameters for DII calculation including some categories of flavonoids, turmeric, thyme, saffron, and others that are usually consumed in small amounts, infrequently, or not consumed at all in the Swedish population; hence, they may not have had a major impact on the scoring. Absence of information on tumor hormone receptor status for the cancer cases, vitamin D status, and body composition status are possible limitations to the study. However, it should be noted that most women in Western populations are receptor positive and the vast majority of postmenopausal women are receptor positive (Palmer *et al*, 2007; Reis-Filho and Tutt, 2008). Another limitation is the absence of a significant trend for association across quartiles. This could be because of the presence of other factors that could contribute to the incidence of BrCa, with hormonal factors being the most important one.

In conclusion, women who consumed a more proinflammatory diet appear to be at increased risk of breast cancer compared with women who consumed an anti-inflammatory diet, especially in postmenopausal women.

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CONFLICT OF INTEREST

Dr James R Hébert owns Connecting Health Innovations LLC (CHI), a company planning to develop DII-based computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr Nitin Shivappa is an employee of CHI.

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