Nutrition and Cancer

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hnuc20

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To cite this article: Bahareh Sasanfar, Fatemeh Toorang, Maedeh Mozafari Nia, Amin Salehi-Abargouei & Kazem Zendehdel (2021): Dietary Inflammatory Index and Breast Cancer: report from a Large-Scale Case-Control Study, Nutrition and Cancer, DOI: 10.1080/01635581.2021.1957489

To link to this article: https://doi.org/10.1080/01635581.2021.1957489

Published online: 05 Aug 2021.

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2021.1957489

Dietary Inflammatory Index and Breast Cancer: report from a Large-Scale Case-Control Study

Bahareh Sasanfar[a,b], Fatemeh Toorang[c,d], Maedeh Mozafari Nia[c], Amin Salehi-Abargouei[a,b] and Kazem Zendehdel[c,e,f]

[a]Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [b]Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [c]Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, Iran; [d]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [e]Cancer Biology Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, Iran; [f]Breast Diseases Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Objective: The relationship between diet, including its inflammatory potential, and breast cancer has led to inconsistent results. We investigated the association between a dietary inflammatory index (DII) and the odds of breast cancer in a large case-control study among women.

Methods: This case-control study was carried out on 412 women with pathologically confirmed breast cancer and 456 apparently healthy controls. DII scores were calculated from dietary intake data. Multi-variable adjusted logistic regression was used to obtain odds ratios for breast cancer across quartiles of DII.

Results: A total participants aged 45 ± 10.8 years were included in the present study. After adjustment for potential confounders, individuals in the highest quartile of DII scores had 1.5 times higher odds of breast cancer than those with the lowest (OR= 1.56; 95%CI: 1.04–2.35, P_{trend}=0.02). Premenopausal women with the greatest DII had higher odds for breast cancer, compared with those with the lowest DII (OR= 1.92; 95% CI: 1.14–3.25, P_{trend}=0.01). No significant association was seen between DII and odds of breast cancer in postmenopausal women.

Conclusion: Dietary inflammatory index might be directly associated with odds of breast cancer particularly in premenopausal women. Prospective cohort studies are needed to confirm these findings.

ARTICLE HISTORY
Received 30 September 2020
Accepted 6 July 2021

Introduction

Breast cancer is the most prevalent cancer among women, worldwide, and the leading cause of female mortality in both developed and developing economies. The number of breast cancer cases is predicted reaching 3,059,829 in 2040 (1). The disease is also the first common cancer among Iranian women and the world health organization (WHO) reported that the age-standardized incidence rate of breast cancer was 31.0 per 100,000 for Iranian women in 2018 (1).

Despite the high prevalence of breast cancer in the world, because of being high heterogeneous of its etiology, certain aspects have not been explicated. Although some risk factors of breast cancer including genetic, race, physical activity, obesity, and environmental carcinogens have been recognized by previous investigations (2), role of dietary factors on the risk of breast cancer is studied inconsistently. Scientific evidence has considered diet as a modifiable risk factor that is responsible for approximately 35% of all cancer incidences. A number of studies have shown the association between inflammation and cancers (3). Also, assessment of dietary factors as agents that might affect inflammation has been considered (4). Previous studies evaluated the association of dietary anti-inflammatory agents such as omega-3, curcumin (5), vitamin D (6), and flavonoids (7) with breast cancer risk. However, these studies have investigated the association of dietary intakes of individual

CONTACT Amin Salehi-Abargouei abargouei@ssu.ac.ir;abargouei@gmail.com;bsasanfar@yahoo.com Department of Nutrition, Faculty of Health, Shahid Sadoughi University of Medical Sciences, Yazd, P. O. Box 8915173160, Iran; Kazem Zendehdel kzendeh@tums.ac.ir Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, P.O. Box 13145158, Iran.

inflammatory or anti-inflammatory agents with cancers, and association of the inflammatory capacity of the diet as a whole has received limited attention. The Dietary Inflammatory Index (DII) has been developed to compute the inflammatory potential of the overall diet and has been validated concerning several inflammatory biomarkers (8, 9). A prospective study illustrated that the intake of a diet whit higher proinflammatory content increases the risk of breast cancer especially in postmenopausal women (10). However, a case-control study indicated that higher DII scores may increase breast cancer risk especially among premenopausal women (11). A meta-analysis suggested a non-significant association between higher DII scores and the likelihood of developing breast cancer (12).

Few studies have been conducted on association of diet and breast cancer in Middle Eastern countries and most data came from non-Asian countries where have unique dietary habits (13) such as high intake of refined grains and fats especially those with harmful effects which have high inflammatory potential and might cause cancers. Previous case-control studies conducted in Iran had a low sample size and did not match participants for their age and geographic location (11, 14). Given the limitation of prior research, assessment of the association between DII and breast cancers among the Middle Eastern population might be of great importance. The present study was conducted to determine the association between DII and the risk of breast cancer in a large case-control study of Iranian women.

Subjects and Methods

Participants

This hospital-based case-control study was carried out among Iranian women aged 19–80 years old between 2014 and 2016. All Patients had pathologically confirmed breast cancer those who had not been diagnosed for more than 1 year.

Eligibility Criteria

The case group was selected from breast cancer patients who had been referred to surgery, chemotherapy or radiotherapy departments of Iran Cancer Institute that is located at a major teaching and general hospital, Imam Khomeini complex in Tehran. They had no history of any other cancers. Control subjects were healthy women admitted to the same hospital as a co-patient in Imam Khomeini hospital. They were selected based on easy sampling and had no long-term dietary restrictions. All controls were matched with cases according to age classification (±10 years) and geographic location. For the current analysis, we excluded 38 participants who had no response to more than 70 items of FFQ and also excluded 35 participants with a total energy intake of more than 5,500 or less than 800 kcal/d from the study. After exclusions, the final sample included 461 cases and 495 controls.

Ethical Approval

The study was approved by the Bioethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Ethics code: 93-03-51-27113), and all participants signed a written informed consent at the beginning of the study.

Assessment of Dietary Intake

A 168-item validated food-frequency questionnaire was administered to all patients by trained interviewers. Participants were asked to designate their intake frequency for each food item consumed on a daily, weekly, or monthly basis. Patients reported their consumption over the previous year. Participants who could not respond to their frequency of consumption based on the values mentioned in the questionnaire, had reported their own portion sizes which were converted to the portion size of the questionnaire. The Daily portion size of reported consumed foods was calculated and then converted to grams. Total energy intake was calculated by summing up the energy from all foods and nutrient content of foods that were analyzed using the USDA food composition database modified for Iranian foods. In a previous study, the validity and reliability of this FFQ was confirmed by comparing the data from 12dietary recalls and two similar FFQs that completed 1 year apart (15, 16).

Assessment of Dietary Inflammatory Scores

The FFQ-derived dietary data was used to calculate energy adjusted Dietary Inflammatory Index (DII) scores for all of the women. Hence, a methods developed by Shivappa et al was applied for this study (8). The DII score was computed for 38 food parameters including: energy, carbohydrate, fat, protein, fiber, cholesterol, mono-unsaturated fatty acids (MUFA), poly unsaturated fatty acids (PUFA), n-3 fatty acids, n-6 fatty acids, saturated fats (SFAs), trans fat,

thiamin, riboflavin, niacin, pyridoxine, folic acid, cobalamin, vitamin A, C, D, E, β-carotene, zinc, selenium, magnesium, iron, caffeine, pepper, onion, garlic, green/black tea, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins and isoflavones. At first, residual method was used for energy adjusted quantities of all 38 nutrients (17). Then, a z-score for all 38 food items was calculated for each individual. This was obtained by subtracting the "standard global mean" from the quantity of food items consumed by each subject and dividing this value by the "global standard deviation". In order to minimize skewness, we converted this value to a centered percentile score via multiplying this score by the effect score for each food parameter obtained from the study done by Shivappa et al. (8). Finally, we calculated overall DII scores from summing all of DII scores calculated for individual food items. The DII scores would theoretically range from −11.01 to +11.01 for the participants. A greater DII score, indicated more inflammatory potential of the diet.

Assessment of Other Variables

Weight was measured, with subjects minimally clothed without shoes, using digital scales and recorded to the nearest 1 kg. Using a tape meter, height was measured in a standing position without shoes, while shoulders were in normal alignment; Body mass index (BMI) was calculated as weight (Kg) divided by height squared (m^2).

The Global Physical Activity Questionnaire (GPAQ) questionnaire was developed by the World Health Organization (WHO) to monitor physical activity in different countries (18). Patients were asked to recall their physical activity habits in the year preceding their cancer diagnosis. This questionnaire contains 16 questions related to physical activity at work, during transportation, recreation and sports activities, and sedentary behavior. The Metabolic Equivalent (MET)-hours per week were calculated based on the published GPAQ Analysis Guide (19). This questionnaire has been carried out in 49 countries including Iran (20). It is proposed that GPAQ might better assess physical activity in developing countries because most activities take place while working and commuting and can provide more precise associations between physical activity and metabolic abnormalities (21).

Additional information on age, educational level, family history of breast cancer, alcohol and tobacco use, marital status, pregnancy history, parity, age at menopause, and contraceptive use were collected through face-to-face interviews by trained interviewers.

Statistical Methods

We categorized all participants based on quartiles of DII scores. We used Student's *t*-test and chi-square test to compare the mean of continuous variables and categorical variables of cases and controls, respectively. Dietary intakes of DII components were compared with global intakes reported by Shivappa et al. (8) using one sample *t*-test. We applied one-way ANOVA and chi-square test to compare variables across quartiles of DII, where appropriate. We calculated age- and energy-adjusted food and nutrient intakes by quartiles of the DII using ANCOVA. The association between the DII and odds of breast cancer was checked by using logistic regression in crude and multi-variable adjusted models. The analyses were first adjusted for age and energy (continuous) in the first model and additionally for educational level (categorical), parity (nulliparous, 1, 2–3, ≥4), oral contraceptive use (yes vs. no), tobacco use (yes vs. no), alcohol use (yes vs. no), marital status (married, not married) in model 2. We further controlled for physical activity (continuous), family history of breast cancer (yes vs. no) and body mass index (continuous) in the third model. All confounders were selected based on recent research (22, 23). The trend of odds ratios across quartiles of DII score was examined by considering the median value of DII score in each category as a continuous variable. *P* values <0.05 were considered statistically significant. The analysis was performed by Stata version 14 (State Corp., College Station, TX).

Results

The DII score in this study ranged from −7.57 (highest anti-inflammatory score) to 8.35 (highest proinflammatory score and the mean DII score was 0.007 (± 2.92). Compared to controls, cases were slightly older, had a lower BMI, and were more likely to have family history of breast cancer. A lower percentage of cases were physically active, married, use oral contraceptives, use postmenopausal hormones, and had alcohol use. Higher DII scores was associated with younger age. There were no other significant differences across categories of the DII score (Table 1).

Compared with controls, cases had higher consumption of energy, carbohydrates, total fats, cholesterol, SFA, MUFA, selenium, refined grains, whole grains, processed meat, fish, nuts, green/black tea.

Table 1. Overall study participant characteristics.

				Dietary inflammatory index quartiles				
	Case ($n=461$)	Control ($n=495$)	p-value	Q1 ($n=239$, <-1.75)	Q2 ($n=239$, -1.75 to 0.22)	Q3 ($n=239$, -0.22 to 1.55)	Q4 ($n=239$, 1.55<)	p-value
Age (years)	46.0 ± 10.31	44.05 ± 11.26	0.0003	46.71 ± 10.36	44.88 ± 10.9	45.52 ± 11.01	42.86 ± 10.84	0.001
BMI (kg/m2)	28.07 ± 5.20	28.87 ± 6.05	0.01	29.12 ± 5.12	28.35 ± 5.58	28.13 ± 6.20	28.31 ± 5.69	0.24
Physical activity (MET-h/week)	23.09 ± 4.80	29.37 ± 44.19	0.01	31.76 ± 45.7	26.77 ± 42.7	23.65 ± 37.0	23.21 ± 44.4	0.10
Age at menarche (years)	13.02 ± 2.54	12.92 ± 2.76	0.28	13.28 ± 1.77	12.82 ± 2.80	13.02 ± 2.73	12.74 ± 3.12	0.11
Menopausal status (%)								
Premenopausal	301(66.59)	325 (67.15)	0.85	147 (63.91)	148 (64.91)	140 (63.93)	161 (70.31)	0.41
Postmenopausal	151(33.41)	159 (32.85)		83 (36.9)	80 (35.09)	79 (36.07)	68 (29.69)	
Educational level (%)								
Un university	379 (83.85)	406 (84.06)	0.93	198 (83.54)	195 (83.33)	193 (83.91)	199 (85.04)	0.96
University	73 (16.15)	77 (15.94)		39 (16.46)	39 (16.67)	37 (16.09)	35 (14.96)	
Marital status (%)								
Married	369 (81.6)	415 (87.0)	0.05	203 (86.3)	188 (81.03)	195 (84.7)	198 (85.34)	0.51
Unmarried/divorced/widowed	83 (18.3)	62 (13.0)		32 (13.6)	44 (18.97)	35 (15.22)	35 (14.66)	
Family history of breast cancer (%)	44 (9.73)	7 (1.42)	0.000	9 (3.80)	16 (6.75)	14 (5.96)	12 (5.06)	0.52
Oral contraceptive use (%)	236 (53.03)	258 (61.43)	0.01	135 (61.09)	117 (54.93)	115 (53.49)	127 (58.80)	0.35
Current smoker (%)	16 (3.54)	24 (4.98)	0.27	15 (15.36)	4 (1.72)	9 (3.90)	12 (5.13)	0.08
Alcohol use (%)	12 (2.65)	29 (6.00)	0.01	13 (5.49)	9 (3.85)	7 (3.04)	12 (5.13)	0.54
Postmenopausal hormone use (%)	2 (0.43)	10 (2.02)	0.02	4 (1.67)	4 (1.67)	1 (0.42)	3 (1.26)	0.56
Parity								
Nulliparous/missing	210 (42.42)	204 (44.25)	0.75	107 (44.77)	102 (42.68)	113 (47.28)	92 (38.49)	0.46
1	51(10.30)	39 (8.46)		21 (8.79)	19 (7.95)	21 (8.79)	29 (12.13)	
2–3	154 (31.11)	147 (31.89)		79 (33.05)	74 (30.96)	73 (30.54)	75 (31.38)	
≥4	80 (16.16)	71 (15.40)		32 (13.39)	44 (18.41)	32 (13.39)	43 (17.99)	

χ2 Test for ordinal qualitative variables and *t*-test for continuous variables.

Cases had also lower intakes of proteins, fiber, PUFA, iron, magnesium, zinc, vitamin B1, B2, B3, B6, B12, B9, A, C, D, E, β-carotene, fruits, vegetables, high fat dairy, legumes and coffee. Dietary intakes of DII components were significantly different from global intakes ($P<0.001$) except for dietary proteins and riboflavin for patients with cancer and riboflavin for healthy participants (Table 2). Higher DII score was related to higher intakes of energy, total fats, carbohydrates, cholesterol, SFA, PUFA, MUFA, selenium and vitamin E as well as lower intake of fiber, magnesium, β-carotene, vitamin B2, B6, B9, C, D and fruits. Individuals in the third quartile of DII had the lowest intake of proteins, iron, zinc, vitamin B1, B3, B12, A, fish, vegetables and high fat dairy (Table 2).

Although no significant association was observed between DII scores and odds of breast cancer in the whole study population in the crude model, those with highest concordance with DII had a higher odds for developing the disease compared to those with lowest DII after controlling for age and energy [odds ratio (OR)= 1.46; 95%CI: 1.00–2.13, P_{trend}=0.04]. This association was strengthened after controlling for further confounders including education, parity, oral contraceptive use, cigar smoking, alcohol consumption and marital status (OR= 1.56; 95%CI: 1.04–2.35, P_{trend}=0.02). However, after adjustment for physical activity, family history of breast cancer, and BMI in the third model this association disappeared (OR= 1.43; 95%CI: 0.94–2.18, P_{trend}=0.11). After stratification of participants based on their menopausal status, we found that premenopausal women in the top category of DII scores had higher odds of breast cancer, compared with those in the bottom category, after adjustment for age and energy intake (OR= 1.76; 95%CI: 1.11–2.79, P_{trend}=0.01). Although this association remained significant when we further controlled for other potential confounders in the second model. After additional adjustment for physical activity, family history of breast cancer, and BMI, those in the top quartile had a marginally significant higher odds of breast cancer than those in the bottom quartile (OR = 1.67; 95%CI: 0.97–2.88) however the increasing trend was still significant (P_{trend} = 0.05). No significant association was seen between DII scores and odds of breast cancer in postmenopausal women, either before or after controlling for confounders. BMI status-stratified analysis for the association between DII scores and risk of breast cancer shown no significant association either in participants with normal weight or overweight/obesity (Table 3).

Discussion

In this study, we found that although higher scores of DII (most proinflammatory diet) was significantly associated with odds of breast cancer in the whole study population after adjustment for age, energy, education, parity, oral contraceptive use, smoking

Table 2. Dietary intakes of participants[a].

	Case ($n=461$)	Control ($n=495$)				Age and energy-adjusted dietary inflammatory index quartiles				
						1 ($n=239$)	2 ($n=239$)	3 ($n=239$)	4 ($n=239$)	
	Mean ± SD	Mean ± SD	*p*-value[b]	*p*-value[c]	*p*-value[d]	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*p*-value[e]
Energy (kcal/d)	2821.3 ± 1034.9	2763.1 ± 1068.5	0.0002	<0.001	<0.001	2672.9 ± 908.2	2485.5 ± 959.2	2621.1 ± 1040.5	3385.1 ± 1060.5	<0.001
Nutrients										
Carbohydrates (g/d)	356.6 ± 139.7	349.8 ± 143.5	<0.001	<0.001	<0.001	359.6 ± 128.7	338.9 ± 138.1	345.6 ± 156.2	368.1 ± 141.2	<0.001
Proteins (g/d)	81.9 ± 32.5	83.9 ± 39.4	<0.001	0.08	0.01	97.3 ± 43.5	80.8 ± 31.2	75.6 ± 32.1	78.2 ± 32.8	<0.001
Total fats (g/d)	125.2 ± 71.2	120.7 ± 69.4	<0.001	<0.001	<0.001	101.2 ± 45.8	95.9 ± 46.8	110.3 ± 57.2	184.0 ± 84.4	<0.001
Fiber (g/d)	26.3 ± 12.1	27.0 ± 13.3	<0.001	<0.001	<0.001	35.0 ± 14.2	26.2 ± 11.1	23.5 ± 12.0	22.0 ± 8.8	<0.001
Cholesterol (mg/d)	190.1 ± 115.3	184.4 ± 101.0	<0.001	<0.001	<0.001	196.0 ± 111.8	179.2 ± 93.9	174.4 ± 97.4	199.0 ± 125.1	<0.001
SFA (g/d)	49.6 ± 34.7	48.02 ± 33.7	<0.001	<0.001	<0.001	36.3 ± 20.4	35.7 ± 21.9	41.8 ± 26.5	81.2 ± 40.7	<0.001
MUFA (g/d)	40.40 ± 25.8	39.35 ± 25.04	<0.001	<0.001	<0.001	32.1 ± 15.9	30.0 ± 15.8	34.8 ± 20.7	62.4 ± 31.0	<0.001
PUFA (g/d)	30.14 ± 18.07	30.50 ± 17.17	<0.001	<0.001	<0.001	31.9 ± 16.2	27.3 ± 15.0	29.5 ± 19.2	32.6 ± 19.1	<0.001
Fe (mg/d)	23.40 ± 10.04	23.78 ± 12.21	<0.001	<0.001	<0.001	27.4 ± 11.5	22.5 ± 11.2	21.9 ± 10.8	22.4 ± 10.3	<0.001
Mg (mg/d)	341.8 ± 108.1	345.5 ± 175.4	<0.001	<0.001	<0.001	443.8 ± 210.3	336.0 ± 133.3	311.9 ± 142.9	283.4 ± 110.4	<0.001
Zn (mg/d)	10.86 ± 4.89	11.41 ± 5.76	<0.001	<0.001	<0.001	13.67 ± 6.03	10.8 ± 4.80	10.04 ± 4.9	10.07 ± 4.7	<0.001
Se (mg/d)	97.34 ± 43.36	96.8 ± 48.8	<0.001	<0.001	<0.001	98.8 ± 41.9	94.7 ± 45.5	94.8 ± 49.2	99.8 ± 47.8	<0.001
Thiamin (mg/d)	1.89 ± 0.73	1.90 ± 0.84	<0.001	<0.001	<0.001	2.25 ± 0.77	1.86 ± 0.78	1.73 ± 0.78	1.76 ± 0.70	<0.001
Riboflavin (mg/d)	1.68 ± 0.78	1.76 ± 0.88	<0.001	0.74	0.11	2.20 ± 0.87	1.68 ± 0.72	1.50 ± 0.79	1.49 ± 0.74	<0.001
Niacin (mg/d)	19.49 ± 8.54	20.11 ± 10.31	<0.001	<0.001	<0.001	22.3 ± 10.5	19.1 ± 8.5	18.2 ± 8.8	19.6 ± 9.5	<0.001
Vitamin B6 (mg/d)	2.20 ± 0.99	2.32 ± 1.09	<0.001	<0.001	<0.001	2.94 ± 1.13	2.21 ± 0.93	1.97 ± 0.93	1.95 ± 0.85	<0.001
Vitamin B12 (mcg/d)	4.46 ± 3.37	4.75 ± 3.68	<0.001	<0.001	0.01	5.91 ± 4.30	4.48 ± 3.20	3.90 ± 2.91	4.16 ± 3.26	<0.001
Folate (mcg/d)	371.6 ± 167.6	383.8 ± 180.1	<0.001	<0.001	<0.001	511.9 ± 197.3	371.1 ± 162.3	322.5 ± 132.7	306.1 ± 112.0	<0.001
β-carotene (mcg/d)	6698.3 ± 4764.5	6858.6 ± 5082.9	<0.001	<0.001	<0.001	9884.2 ± 6403.1	6746.1 ± 4595.8	5443.2 ± 3345.6	5051.8 ± 3120.8	<0.001
Vitamin A (RE/d)	1112.9 ± 621.9	1145.5 ± 673.1	<0.001	<0.001	<0.001	1523.9 ± 779.8	1114.9 ± 631.5	939.5 ± 459.1	940.9 ± 493.0	<0.001
Vitamin C (mg/d)	264.8 ± 149.3	281.7 ± 175.5	<0.001	<0.001	<0.001	395.7 ± 185.7	271.6 ± 156.3	227.3 ± 125.2	199.5 ± 100.4	<0.001
Vitamin E (mg/d)	23.2 ± 13.2	23.8 ± 13.7	<0.001	<0.001	<0.001	24.3 ± 12.98	20.7 ± 11.23	22.6 ± 15.39	26.3 ± 13.46	<0.001
Vitamin D (mcg/d)	2.87 ± 3.29	2.93 ± 3.20	<0.001	<0.001	<0.001	4.09 ± 4.57	2.91 ± 2.64	2.35 ± 2.63	2.27 ± 2.30	<0.001
Food groups				–	–					
Refined grains (g/d)	338.2 ± 200.6	316.2 ± 184.4	<0.001	–	–	279.7 ± 157.8	295.4 ± 162.2	338.1 ± 208.4	394.2 ± 215.1	<0.001
Whole grains (g/d)	97.5 ± 103.4	96.4 ± 111.7	<0.001	–	–	78.6 ± 73.52	101.9 ± 109.5	98.9 ± 119.5	108.2 ± 120.0	<0.001
Processed meats (g/d)	4.09 ± 12.06	2.57 ± 5.04	<0.001	–	–	3.21 ± 10.8	3.34 ± 10.4	2.93 ± 7.27	3.71 ± 7.51	<0.001
Fish (g/d)	14.7 ± 20.6	13.9 ± 20.9	<0.001	–	–	19.74 ± 27.1	15.48 ± 19.51	11.01 ± 18.2	11.08 ± 15.3	<0.001
Fruits (g/d)	578.5 ± 397.2	592.7 ± 396.1	<0.001	–	–	808.5 ± 446.7	589.0 ± 378.3	501.0 ± 347.2	445.0 ± 301.1	<0.001
Vegetables (g/d)	346.4 ± 255.0	364.2 ± 233.7	<0.001	–	–	504.1 ± 306.1	352.5 ± 214.0	278.8 ± 180.4	287.0 ± 185.8	<0.001
High fat dairy (g/d)	382.1 ± 278.1	409.8 ± 311.4	<0.001	–	–	479.6 ± 310.3	386.6 ± 270.7	349.9 ± 271.8	369.6 ± 313.3	<0.001
Legumes (g/d)	48.5 ± 52.08	52.3 ± 79.1	<0.001	–	–	74.2 ± 109.2	52.5 ± 51.8	40.7 ± 42.8	34.5 ± 29.3	<0.001
Nuts (g/d)	15.28 ± 22.04	14.39 ± 19.8	<0.001	–	–	18.34 ± 21.8	14.87 ± 19.33	16.48 ± 26.93	9.59 ± 11.49	<0.001
Black tea (g/d)	746.5 ± 659.2	744.7 ± 964.1	<0.001	–	–	1020.2 ± 1244.9	702.5 ± 683.1	638.0 ± 584.7	620.4 ± 552.7	<0.001
Coffee (g/d)	9.13 ± 45.05	21.45 ± 135.4	0.04	–	–	17.99 ± 61.9	13.46 ± 73.2	16.77 ± 92.4	13.84 ± 156.6	0.37

[a]All values were adjusted for age and energy, except for dietary energy intake, which was only adjusted for age using ANCOVA.
[b]*P*-values for comparison between case and control groups.
[c]*P*-values for comparison between dietary intakes of participants with cancer and global mean daily intakes reported by Shivappa *et al.* (8).
[d]*P*-values for comparison between dietary intakes of healthy participants and global mean daily intakes reported by Shivappa *et al.* (8).
[e]*P*-values for comparison across inflammatory index quartiles.

Table 3. Risk for breast cancer according to quartiles of the dietary inflammatory index with stratification by menopausal status and body mass index (BMI).

	OR (95% CI)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Total					P_{Trend}[a]
No. of cases/controls (412/456)	108/131	110/129	116/123	127/112	
Crude	1	1.03 (0.72–1.48)	1.14 (0.79–1.63)	1.37 (0.95–1.97)	0.06
Model 1	1	1.10 (0.76–1.60)	1.20 (0.83–1.73)	1.46 (1.00–2.13)	0.04
Model 2	1	1.07 (0.72–1.59)	1.09 (0.74–1.61)	1.56 (1.04–2.35)	0.02
Model 3	1	1.03 (0.68–1.55)	1.05 (0.70–1.56)	1.43 (0.94–2.18)	0.11
Premenopause					
No.of cases/controls (267/300)	67/82	70/79	73/76	88/61	
Crude	1	1.08 (0.68–1.71)	1.17 (0.74–1.85)	1.76 (1.11–2.79)	0.01
Model 1	1	1.16 (0.73–1.85)	1.22 (0.77–1.94)	1.87 (1.15–3.02)	0.01
Model 2	1	1.17 (0.71–1.93)	1.14 (0.70–1.87)	1.92 (1.14–3.25)	0.01
Model 3		1.10 (0.65–1.86)	1.08 (0.65–1.81)	1.67 (0.97–2.88)	0.05
Postmenopause					
No.of cases/controls (145/147)	38/40	38/39	35/43	40/37	
Crude	1	1.02 (0.54–1.92)	0.85(0.45–1.60)	1.13 (0.60–2.13_	0.77
Model 1	1	1.00 (0.53–1.89)	0.84 (0.45–1.60)	1.18 (0.61–2.26)	0.69
Model 2	1	0.90 (0.45–1.80)	0.71 (0.35–1.40)	1.27 (0.63–2.57)	0.62
Model 3	1	0.85 (0.41–1.73)	0.69 (0.34–1.39)	1.11 (0.54–2.29)	0.88
BMI < 25(kg/m^2)					
No.of cases/controls (129/121)	25/38	35/27	34/29	35/27	
Crude	1	1.97 (0.96–4.01)	1.78 (0.87–3.61)	1.97 (0.96–4.01)	0.09
Model 1	1	2.25 (1.08–4.69)	2.05 (0.99–4.26)	1.93 (0.91–4.08)	0.09
Model 2	1	2.77 (1.21–6.37)	1.99 (0.89–4.45)	2.25 (0.95–5.32)	0.07
Model 3	1	2.73 (1.16–6.41)	1.70 (0.73–3.94)	2.02 (0.84–4.88)	0.16
BMI ≥ 25(kg/m^2)					
No.of cases/controls (332/374)	85/92	75/101	80/97	92/84	
Crude	1	0.80 (0.52–1.22)	0.89 (0.58–1.35)	1.18 (0.78–1.79)	0.36
Model 1	1	0.83 (0.54–1.27)	0.90 (0.59–1.39)	1.26 (0.81–1.96)	0.30
Model 2	1	0.80 (0.51–1.27)	0.76 (0.48–1.20)	1.36 (0.85–2.17)	0.34
Model 3	1	0.78 (0.49–1.24)	0.76 (0.48–1.21)	1.31 (0.81–2.12)	0.38

[a]Trend based on median values of each quartile.
Model 1: Adjusted for age and energy.
Model 2: further adjusted for education, parity, oral contraceptive use, cigar smoking, alcohol consumption, marital status.
Model 3: This model was additionally adjusted for physical activity, family history of breast cancer, menopausal status and BMI (continuous) for total participants. Variables used for stratification were not adjusted in this model.

cigarette, alcohol use, and marital status; this association vanished after considering further variables including physical activity, family history of breast cancer, and BMI in the model. After stratifying according to menopausal status also a trend toward significant positive association was seen between DII scores and odds of breast cancer in premenopausal women. This association was independent of potential confounders. To our knowledge, this is the first large study examining the relationship between DII and risk of breast cancer in a Middle-Eastern countries.

The relation between diet as well as nutrients with breast cancer has been examined about consumption of fruits, vegetables, coffee, green tea, vitamin D, flavonoids as antiinflammatory components and carbohydrate, processed meat, saturated fats, iron as proinflammatory components (24, 25). Other studies examined risk of breast cancer with dietary patterns like Mediterranean diet, DASH diet, healthy diet and vegetarian diet and showed conflicting results (26, 27). As DII considers dietary intakes of all anti and proinflammatory index giving us the possibility to evaluate the overall scores of inflammatory potential from a wide source of foods in the diet. Previous studies investigated the association between DII and several outcomes (28–30). In terms of breast cancer and DII two case-control studies with small sample size indicated positive relation among Iranian women (11, 14). Several studies of breast cancer and DII have been applied in other regions. In a prospective study conducted in Swedish women, a marginal significant association was observed between DII score and risk of breast cancer in overall participant (RR = 1.18; 95%CI: 1.00–1.39, $P = 0.07$) and a stronger association in postmenopausal women (RR = 1.22; 95%CI: 1.01–1.46, $P = 0.03$) (31). A large Italian case-control study indicated a positive association between DII and breast cancer risk in all participants (OR = 1.75; 95%CI: 1.39–2.21, $P < 0.001$) and in postmenopausal women (OR = 1.85; 95%CI: 1.38–2.48, $P = 0.007$) (32). Another case-control study among Chinese women showed positive association between DII and odds of breast cancer in whole (OR = 1.40; 95 CI, 1.25–1.39, $P < 0.001$), pre- (OR = 1.50; 95 CI, 1.30–1.73, $P < 0.001$) and

post-menopausal women (OR = 1.27; 95 CI, 1.06–1.53, $P = 0.01$) (33). In this study, we observed that after adjusting for some confounders, whole and premenopausal women with higher DII scores had 1.5 and 1.9 times higher odds of breast cancer than those with the lowest DII scores, respectively. This association was not significant among postmenopausal women. In contrast to our findings, the study done in China showed a positive association between breast cancer risk in overweight and obese women (33). In some studies, the DII and breast cancer has been evaluated in postmenopausal women only. A population–based case-control study on postmenopausal women living in Germany found no significant association between DII and breast cancer risk (34). Also Woman's Health Initiative applied in US could not show any association between DII and breast cancer (35). In contrast to previous studies, an analysis of Iowa Women's Health prospective study, showed a positive relationship between DII scores and breast cancer risk after 25 years of follow-up (RR = 1.11; 95 CI, 1.00–1.22, $P = 0.06$) (10). The different findings might be attributable to the differences in DII scores in the populations of the studies. Mean DII scores in the Chinese (-1.48 ± 1.78) reveals more anti-inflammatory diet than Iranian population (0.007 ± 2.50) in present study. Energy adjusted DII scores were not used in Italian, Swedish and US studies. On the other hand, the number of anti or pro-inflammatory food items used to assess the DII score were different between the previous investigations. The number of food items to calculate dietary DII score ranged between 25 to 34 food items (11, 31–35). It should be noted that compared to other studies we considered more components (38 food parameters). However, it is proposed that the range of DII may be more dependent on the amount of food consumption than on the number of available component (35).

The positive association of the DII with risk of breast cancer in the present study may arise through the effect of a proinflammatory diet on levels of inflammatory cytokines and chemokine that promote tumor initiation, growth and invasion (36). Interleukins, especially IL-6, stimulate production of C-reactive protein as a marker of inflammation (9). IL-6 is responsible for induction of CTEN and fascin both of which are important factors in breast cancer cell migration and invasion (37). Insulin-like growth factor (IGF-1R) and insulin are regulated by both IL-6 and dietary consumption, play roles in tumor growth factors, antiapoptotic activities, and hormonal environment changes (38, 39). Another mechanism is via ω-6 fatty acids like arachidinic acid which produce prostaglandins and leukotriesnes that are key mediators of inflammation. Arachidonic acid stimulate the production of PPARβ/δ that leading overproduction of prostaglandin E2. In contrast, PPARα as an anti-inflammatory factor is inhibited by estrogen (40, 41). These findings are in line with our result that associations are stronger in premenopausal cancer women, who have higher activation of hormonal factors.

The strengths of our study include large sample size, the use of validated questionnaires for dietary assessment, controlling for several potential confounders, recruiting participants from a referral hospital, in which subjects are from the whole country, doing stratified analysis by menopausal status and using 38 (of 45) food parameters to compute the DII. However, several limitations need to be considered. First, results from case-control design of the study have inherent limitations of recall and selection bias, which can prohibit us inferring causality. Second, as with all epidemiologic studies, even validated FFQs are prone to misclassification. Misclassification lead to underestimation of risk estimates; therefore, the true effect might be stronger. Third, we lacked data on hormone receptor status, which might intermediate the association between diet and the risk of breast cancer.

Conclusion

We found that more proinflammatory dietary intakes might associated with increased odds of breast cancer, especially among premenopausal women. Further research, especially cohort studies are needed to confirm these results.

Author's Contributions

BS and FT participated in the study design, analysis and drafted the initial version. FT and MMN helped in data analysis. BS implemented comments and suggestions of the coauthors. KZ and ASA contributed in conception, design and data analysis. All authors reviewed the final version of the manuscript. KZ and AS supervised the study.

Acknowledgments

We would like to express our special thanks to the participants, without whom the study would not have been possible

Availability of Supporting Data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for Publication

There is no personal information regarding any patients in our article.

Disclosure Statement

None of the authors declared any conflicts of interest.

Ethical Approval and Consent to Participate

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Tehran University of Medical Sciences. Written informed consent was obtained from all subjects/patients

Funding

This study was financially supported by the Cancer Research Center of Tehran University of Medical Sciences (no. 93-03-51-27113).

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