Inflammatory potential of diet in association with breast cancer risk: A matched case-control study

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Research article

Keywords: Breast cancer, Dietary inflammatory index, Diet, Hormone receptors, Molecular subtypes, Luminal phenotype, HER2-enriched, Triple-negative.

Posted Date: August 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-57681/v1

Abstract

Background: The present study aimed to explore the association between the dietary inflammatory index (DII $^{®}$) and the risk of different molecular subtypes of breast cancer (BrCa) for the first time in a large population-based case-control study conducted in Iran.

Methods: The subjects consisted of 1007 women with histopathologically confirmed BrCa, and 1004 controls admitted to hospitals in Tabriz, Iran, for non-neoplastic conditions. The DII scores were computed based on dietary intake collected using a validated 136-item food frequency questionnaire. Energy-adjusted DII (E-DII ^{TM}) also were calculated. Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs).

Results: The pro-inflammatory diet [highest E-DII quartile (Q)] vs. the anti-inflammatory diet (lowest E-DII scores) showed significantly increased BrCa risk (OR $_{Q4\ vs.\ Q\ 1}$: 1.87; 95% CI: 1.42–2.47). This was aligned with the findings obtained in women at reproductive ages (premenopausal status) who diagnosed with luminal A [estrogen receptor-positive (ER $^{+}$) and/or progesterone receptor-positive (PR $^{+}$) and human epidermal growth factor receptor 2-negative (HER2 $^{-}$)] (OR $_{Q4\ vs.\ Q\ 1}$: 2.71; 95% CI: 1.74–4.22) and luminal B (ER $^{+}$ and/or PR $^{+}$, HER2 $^{+}$) (OR $_{Q4\ vs.\ Q\ 1}$: 2.86; 95% CI: 1.39–5.89). Women in the highest E-DII quartile were three times more likely to have triple-negative BrCa (ER $^{-}$, PR $^{-}$, HER2 $^{-}$) compared to luminal A (OR $_{Q4\ vs.\ Q1}$: 3.00; 95% CI: 1.002–8.96). Likewise, the risk of HER2-enriched BrCa (ER $^{-}$, PR $^{-}$ and HER2 $^{+}$) vs. luminal B subtype was increased among those consumed the most pro-inflammatory E-DII (OR $_{Q4\ vs.\ Q1}$: 2.44; 95% CI: 1.01–5.88). A significant ascending trend was observed in mean E-DII scores, followed by rising tumor size (P=0.018).

Conclusions: The pro-inflammatory diet, as indicated by increasing E-DII scores, was a risk factor of BrCa in Iranian women, providing updates to the invasive molecular subtypes of BrCa. Diets modulated for high anti-inflammatory and low pro-inflammatory dietary components are suggested to prevent the risk of more aggressive forms of BrCa.

Background

Breast cancer (BrCa) is the most common malignancy diagnosed among women in different populations (1). It is the second cause of female cancer mortality worldwide (1). Recently, the incidence of BrCa has rapidly grown among Iranian women and occurs at least a decade earlier than their afflicted counterparts in the developed countries (2). The age-standardized incidence rate for BrCa in Iran was 18.4/100,000/year in 2008 (GLOBOCAN, 2008) (3), which increased rapidly to 28.1/100,000/year in 2012 (GLOBOCAN, 2012) (4). Because the Iranian population has experienced a transition in lifestyle (5), dietary factors could play a prominent role in the etiology of BrCA and rapid increase in incidence in the recent past.

The contribution of inflammatory mediators as a modifiable risk factor for carcinogenesis was first speculated by Rudolf Virchow, who described the presence of leukocytes within neoplastic tissues (6). Today, a persistent, chronic state of low-grade inflammation is a well-known risk factor for developing cancer (7). Chronic inflammation, and even low-grade but long-lasting exposure to inflammation are crucial risk factors that could promote BrCa initiation and development (8). Inflammation provides a substrate for key process in breast tumorigenesis, particularly involved in the development of advanced pathologic BrCa phenotypes (6).

It is well-established that estradiol (E2) is a prominent growth factor inducing estrogen receptor (ER)-dependent BrCa proliferation (9). The pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), drive BrCa cell growth by inducing activation on aromatase, estradiol 17β-hydroxysteroid dehydrogenase (HSD17β1), and steroid sulfatase (10). Therefore, it is imperative to establish epidemiological models incorporating reproductive backgrounds, in connection with inflammation, to reveal BrCa pathogenesis.

In a meta-analysis that reviewed the results of 46 observational epidemiologic studies conducted to elucidate the association between dietary patterns and inflammatory biomarkers, it was found that Western and meat-based dietary patterns were positively associated with chronic inflammation (11). In contrast, fruit- and vegetable-based patterns were inversely correlated with the levels of inflammatory markers (11). Although previous studies considered either the pro- or anti-inflammatory contribution of a single food item on inflammatory biomarkers, the dietary inflammatory index (DII®) was developed to evaluate the inflammatory potential of an individual's whole diet (12). The DII score quantifies the inflammatory potential of an individual's diet in order to provide a more comprehensive picture for interpreting the inflammatory effects of multiple dietary variables (12). To date, relatively few studies have evaluated the association between the energy-adjusted DII (E-DII™) and BrCa risk (13, 14). While most published data on DII scores have excluded dietary supplements in the computation of DII scores; it could be important to consider the anti-inflammatory effects of supplements (15, 16). The quantity, type, and number of supplements included could be important for the calculation of DII.

Previous studies have shown positive associations between the inflammatory potential of diet and risk of different malignancies, including colorectal (17), pancreatic (18), prostate (19), and epithelial ovarian cancers (20). Although several prospective cohorts (21, 22) and case—control studies (23, 24) have indicated a positive association between DII score and risk of BrCa, some studies did not report significant findings (13, 14). There are a few reports on the positive association between the DII and BrCa risk in Iran, particularly among premenopausal women (25). In addition, evidence correlating BrCa risk with DII among women in the Middle East and Iran has not yet been supported by a large population-based study. Moreover, the Iranian dietary pattern is different from that observed in Western countries (26). Importantly, there is no evidence regarding the DII in association with histopathological phenotypes of BrCa.

Therefore, the present study; i.e., the most extensive case–control study among women newly diagnosed with BrCa in Northwestern Iran, aimed to investigate whether the inflammatory potential of diet assessed at diagnosis, using the DII and E-DII scores (both considering and ignoring supplements when computing DII scores), to determine if diet-associated inflammation is associated with BrCa risk.

Methods

Study population

This Breast Cancer Risk and Lifestyle (BCRL) study is a prospective large multicenter cohort study consisting of a consecutive case-series of breast cancer patients who were histopathologically diagnosed with primary malignancy. The study is designed to assess lifestyle-related factors in association with breast cancer risk prevention in northwestern Iran. The current study is a part of this cohort with ongoing recruitment, which began in May 2009. The case group consists of participants with newly diagnosed and histologically confirmed BrCa (n = 1007), who were admitted to the surgical wards of Noor-Nejat Hospital, Shams Hospital, Shahid Ghazi Educational-Oncology Hospital and several oncology clinics located in Tabriz, Iran from May 2009 to January 2018. These are referral hospitals for oncologic surgeries, with patients from different provinces in Northwestern Iran (East and West Azerbaijan, Ardabil, Hamadan, and Zanjan). The participants were native to these provinces or were long-term residents (i.e., had lived there for at least 10 years). Eligible cases were females mainly 27–70 years of age (14 cases were 19–27 years of age), with no previous history of neoplasm at another anatomic site, no history of cystic abnormalities and/or benign breast disease, and no history of adjuvant or neoadjuvant therapy (radiotherapy, chemotherapy, hormonal therapy, and trastuzumab). Patients at stage IV cancer was excluded, according to the TNM staging method (27). The controls were 1004 healthy women, mostly aged 27–70 years of age (11 controls were 19–27 years of age), admitted to the same hospitals during the same period, from hospital wards of orthopedics, ear-nose-throat, ophthalmology surgery, plastic surgery, and healthy women who were caregivers of these non-malignant patients. The controls were healthy women without any medical history of neoplasms, or disorders resulting in considerable metabolic changes. The controls were randomly selected and matched to cases on age at diagnosis (± 2 years) and the study region at a ratio of 1:1 (case: control).

The general inclusion criteria for both the case and control groups consisted of not following specific dietary patterns (vegetarian, DASH, homeopathy, and so on) within 12 months before BrCa diagnosis for the case group and interview for the control group; not currently pregnant, breastfeeding or postpartum at the time of enrollment; having no previous or recent occurrence of chronic inflammatory disorders (gastritis, colitis, multiple sclerosis, lupus erythematosus, and severe rheumatologic disorders); no former or recent occurrence of acute or chronic disease (such as severe liver or kidney failure, hyperthyroidism, and polycystic ovary syndrome); and not being a long-term consumer of aspirin, glucocorticoids, methotrexate, anticonvulsants, sulfasalazine, and contraceptive drugs. The participant with an oophorectomy history reflected the early menopausal status and was excluded. Very active or sedentary subjects and those with morbid obesity (BMI > 45 kg/m^2) were excluded from the present study.

Data collection

General data

A face-to-face interview for each participant was conducted before the surgery by an expert interviewer using a structured questionnaire. The general questionnaire consisted of items regarding sociodemographic characteristics, reproductive variables, medical history, family history of BrCa, and records of dietary supplements and medicines.

Histopathological data

Pathological data for BrCa patients, including histological subtypes (invasive-ductal or invasive-lobular carcinoma), histological grade (I, II, III), tumor size (cm) and immunohistochemistry (IHC) data, including estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2-neu) were collected by reviewing the medical records of patients' pathological examinations. The pathologist fixed the tumor specimens in 10% buffered formalin and prepared formalin-fixed paraffin-embedded tumor blocks. The IHC staining was conducted through the application of antibodies on tumor sections, primarily deparaffinized and incubated at 8ºC overnight. The percentage of stained cells by the antibodies was examined using a binocular microscope (Zeiss KF2 binocular, Germany). HER2 positivity was determined when the membrane/membrane plus cytoplasm stained by antibody (A0485, 1/200; Dako Denmark A/S) accounted for ≥ 10% of tumor cells (28). The Clone ID5 (Dako Denmark A/S) antibody (Glostrup, Denmark) was applied to detect the frequency of cells with ER positivity. Similarly, the IHC staining using Clone PgR636 (Dako Denmark A/S) antibody (Glostrup, Denmark) was applied for PR staining. The protein expression status of ER and PR > 5% were taken into account to identify the positivity of HR (29). The BrCa phenotypes were classified into four molecular subtypes based on IHC data, according to Parise et al. (30) as follows: luminal A (ER + and/or PR+, HER2-), luminal B (ER + and/or PR+, HER2+), triple-negative (ER-, PR-, HER2-), and HER2-enriched (ER-, PR-, HER2+).

Nutritional data

Dietary data were collected using a validated semi-quantitative 136-item food frequency questionnaire (FFQ) (31–34). Portion sizes and frequency of consumption were requested for each food item on a daily, weekly, monthly, or yearly basis. The portion size was defined based on common household utensils provided for each food item. Food portion sizes were converted to grams using standard reference values (35). The timing of FFQ questioning covered up to a year before diagnosis for cases or the control's hospital admission. The intake levels of total energy and nutrients were obtained using Nutritionist IV software (version 3.5.2; 1994, N-Squared Computing, San Bruno, CA, USA) (31). The flavonoid contents of each food and beverage for five major classes of flavonoids (flavanols, flavones, flavonols, flavanones, and anthocyanidins) were calculated using a database developed by the US Department of Agriculture (36).

Dietary inflammatory index (DII®)

The DII is a tool to assess the inflammatory effects of the diet, which was generated by articles assessing the effect of specific food parameters on inflammatory biomarkers (12). Briefly, DII development was

carried out by reviewing and scoring the eligible articles of different type of studies (1943 articles), which investigated diet (foods and dietary ingredients) in association with inflammatory biomarkers such as Interleukins 1β, 4, 6, and 10 (IL-1β, IL-4, IL-6, and IL-10), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). The specific inflammatory scores were computed for all of the constituents of DII, i.e., up to 45 dietary parameters, which included macronutrients, micronutrients, and bioactive components, such as spices, tea, and flavonoids. The estimation of the global mean intake and global standard deviation of each food parameter was calculated using 11 dietary datasets from different countries around the world. The dietary data of each participant was standardized to the global database and exposure relative to the global mean defined as a z-score. The z-score was calculated by subtracting the global mean from the mean of reported dietary intake. For this study, we used the energy-adjusted DII (E-DII™), which describes exposure per 1000 calories for each food parameter. To compute E-DII scores, we used an energy-adjusted global comparative database. To decrease the right skewing, the z-score value of each food parameter was converted to a proportion and this was centered by doubling and subtracting 1. Finally, to obtain the overall E-DII score for each subject, all of the individual E-DII scores for each food parameter were added together. In the present study, data were available for 39 of the 45 food parameters assigned as a component of DII, including energy, carbohydrate, protein, fiber, total fat, monounsaturated fat, polyunsaturated fat, saturated fat, n-3 fatty acids, n-6 fatty acids, cholesterol, vitamin A, vitamin D, vitamin E, thiamin, riboflavin, niacin, vitamin B_6, vitamin B_{12}, vitamin C, folic acid, b-carotene, iron, zinc, magnesium, selenium, caffeine, green/black tea, garlic, onion, saffron, turmeric, pepper, ginger, flavan-3-ol, flavones, flavonols, flavanones, and anthocyanidins. Food items consisting of isoflavones, thyme, rosemary, trans-fat, eugenol, and caffeine were not included in the DII calculation. The inflammatory effect of energy was not considered in E-DII calculation, as the score itself accounted for energy. Moreover, we computed the E-DII both with and without considering the inflammatory effects of dietary supplements. In the present study, the dietary supplements included in the calculation of DII (i.e., DII-s) and E-DII (i.e., E-DII-s) scores consisted of vitamins A, B_1 (thiamin), B_2 (riboflavin), B_3 (niacin), B_6 (pyridoxine), B_{12} (cobalamin), C (ascorbic acid), B_9 (folic acid), D (cholecalciferol), E (α-tocopherol), and K, and iron, zinc, selenium, and magnesium.

Statistical analysis

The Kolmogorov-Smirnov test and plotting histogram techniques were used to evaluate the normal distributions of variables. Accordingly, graphing the box-plots helped remove outliers. Continuous variables were compared between cases and controls by independent sample t-tests. Relative frequencies of categorical variables were compared by performing the chi-squared test. Stratifications based on quartiles were carried out for DII and E-DII in the healthy population. The mean values of variables with multiple sub-groups were compared using analysis of variance (ANOVA). The odds ratios (ORs) and 95% confidence intervals (CIs) were obtained to present the association of DII (including supplements and none) and E-DII (including supplements and none) with BrCa risk, using conditional logistic regression models, conditioned on age (± 2 years) and region of residence. Multivariable regression analyses were carried out by controlling the effect of potent confounders, including BMI, energy intake, type II diabetes history, age at first pregnancy, breastfeeding history, menopause status, sum duration of breastfeeding,

the average duration of each lactation, lactation number, abortion history, age at menarche, pregnancy number, first-degree family history of BrCa, oral contraceptive use, anti-lipid medicines, and x-ray exposure. Subgroup analyses of the present study were based on the findings of previous studies that developed a primary hypothesis of association between inflammation and estrogen (10, 37). Statistical models were stratified by menopausal status, molecular subtypes, HR status, pathological characteristics (tumor grades, and tumor size), and histological subtypes of BrCa. Subgroup analyses were conducted using logistic regression models. The analysis of covariance (ANCOVA) with Bonferroni correction was performed to compare DII and E-DII between tumor size classifications. All statistical analyses were performed using SPSS® 13.0 (SPSS Inc., Chicago, IL, USA). All P-values were based on two-tail tests, and a P-value < 0.05 was considered statistically significant.

Results

General characteristics of the participants

The general characteristics of the participants in the case and control groups are summarized in Table 1. Participants with BrCa had higher total caloric intake (2607.76 ± 1007.63 kcal/d) than the controls (2436.84 ± 897.65 kcal/d, P < 0.001). The case group also had higher (more pro-inflammatory) E-DII scores (-1.13 ± 1.89) compared to the controls (-1.56 ± 1.75, P < 0.001). Likewise, E-DII-s (including supplementation) (-3.37 ± 1.52) was attained higher scores than controls (-3.63 ± 1.36, P < 0.001; Table 1). Among healthy controls, the DII plus supplements (DII-s) was more anti-inflammatory than without supplements (-4.25 ± 1.23 vs. -2.45 ± 1.81, Table 1). Among cases, the DII score was more pro-inflammatory than DII-s (-2.41 ± 1.88 vs. -4.19 ± 1.34, Table 1). Having at least one first-degree relative with BrCa was found to be a frequent pedigree among the participants with BrCa compared to the controls (P < 0.001, Table 1). The incidence of type 2 diabetes mellitus was much more frequent among the cases than the controls (P < 0.001). High visceral fat, defined by the waist-to-hip ratio, and larger body frame, defined by the height-to-waist ratio, were observed at a higher rate in the BrCa group compared to the controls (P < 0.001, Table 1). The relative frequency of reproductive factors was compared between the cases and controls and is presented in Supplementary Table 1.

Table 1
General characteristics of BrCa cases and controls- Breast Cancer Risk and Lifestyle (BCRL) study- Northwestern Iran 2009.

	Cases (n = 1007)		Controls (n = 1004)		
Characteristics	**Mean**	**S.D.**	**Mean**	**S.D.**	**P-value***
E-DII	-1.13	1.89	-1.56	1.75	< 0.001
E-DII including supplements	-3.37	1.52	-3.63	1.36	< 0.001
DII	-2.41	1.88	-2.45	1.81	0.626
DII including supplements	-4.19	1.34	-4.25	1.23	0.308
Total energy intake (kcal/day)	2607.76	1007.63	2436.84	897.65	< 0.001
Age (years)	46.6	9.32	45.96	8.56	0.109
	n	**%**	**n**	**%**	**P-value****
BMI (kg/m^2)					
< 25	229	24.3	268	28.4	0.101
25 to < 30	419	44.5	384	40.7	
≥ 30	293	31.1	292	30.9	
WHR					
< 0.85	302	30.0	432	43.0	< 0.001
≥ 0.85	557	55.3	467	46.5	
Unknown	148	14.7	105	10.5	
Ht/rc					< 0.001
< 10.1	672	77.2	587	66.8	
10.1 to < 11	155	17.8	239	27.2	
≥ 11	44	5.1	53	6.0	
Residence					
City	627	67.9	693	69.1	0.088
Town	297	29.8	273	27.2	
Rural	4	0.4	13	1.3	
Other	19	1.9	24	2.4	

	Cases (n = 1007)		Controls (n = 1004)		
First degree family history of breast cancer					
Yes	34	3.4	11	1.1	< 0.001
No	417	41.4	491	48.9	
Unknown	556	55.2	502	50.0	
Type-2 diabetes					
Yes	60	6.0	15	1.5	< 0.001
No	658	65.3	685	68.2	
Unknown	289	28.7	304	30.3	
	n	**%**			**P-value*** **
Tumor size (cm)					
≤ 2	244	33.9	-	-	< 0.001
2 to ≤ 5	408	56.8	-	-	
> 5	67	9.3	-	-	
Tumor grade					
I	98	16.4	-	-	< 0.001
II	381	63.7	-	-	
III	119	19.9	-	-	
Hormone receptor (HR)					
Positive	632	62.8	-	-	< 0.001
Negative	120	11.9	-	-	
Unknown	255	25.3	-	-	
Molecular subtypes					
Luminal A (LA)	416	41.3	-	-	< 0.001
Luminal B (LB)	142	14.1	-	-	
HER2-enriched	57	5.7	-	-	
Triple negative	61	6.0	-	-	
Unknown	331	32.9	-	-	

	Cases (n = 1007)	Controls (n = 1004)

n: number, S.D.: standard deviation, %: percentage, DII: dietary inflammatory index, E-DII: energy-adjusted DII, BMI: body mass index, WHR: waist to hip ratio and Ht/rc: height to wrist ratio.

The distribution of hormone receptors between case group were as follow: Estrogen receptor (ER): n (%), Progesterone receptor (PR): n (%) and Human epidermal growth factor receptor (HER2): n (%)

ER+: 614 (61%), ER-: 156 (15.5%) and unknown: 237 (23.5%)

PR+: 581 (57.7%), PR-: 171(17.0%) and unknown: 255 (25.3%)

HER2+: 201 (20.0%), HER2-: 478 (47.5%) and unknown: 328 (32.5%)

*T-test was performed to compare the mean (S.D.) of values between BrCa cases and controls.

**Chi-square test was performed to compare relative frequencies through strata between BrCa cases and controls.

***Non parametric chi-square test was performed to compare relative frequencies through strata only among BrCa cases.

DIIs and BrCa risk

Table 2 summarizes the crude and multivariate-adjusted ORs and 95% CIs of BrCa risk according to the quartiles characterized by DII and E-DII (with and without supplements). The multivariable-adjusted model showed a positive association between DII and the risk of BrCa ($OR_{Q3\ vs.\ Q1}$: 1.57; 95% CI: 1.15–2.13) and ($OR_{Q4\ vs.\ Q1}$: 1.56; 95% CI: 1.11–2.18, P_{trend} = 0.021). In a multivariable model, E-DII was positively associated with BrCa risk ($OR_{Q3\ vs.\ Q1}$: 1.47; 95% CI: 1.11–1.94 and $OR_{Q4\ vs.\ Q1}$: 1.87; 95% CI: 1.42–2.47, P_{trend} < 0.001). Moreover, diets with the highest inflammatory scores of DII-s were associated with increased risk of BrCa ($OR_{Q4\ vs.\ Q1}$: 1.43; 95% CI: 1.06–1.92). Individuals in the highest quartile of the E-DII-s score were at higher risk of BrCa in the multivariable model ($OR_{Q4\ vs.\ Q1}$: 1.94; 95% CI: 1.42–2.65; P_{trend} = 0.001).

Table 2
Associations between DII and E-DII and BrCa risk among 1007 cases and 1004 controls.

	Quartiles of DII and E-DII				
	Q1	**Q2**	**Q3**	**Q4**	**P-value for trend**
DII	< -3.83	-3.83 to < -2.74	-2.74 to < -1.2	-1.20 ≤	
DII score mean (S.D.)	-4.52 (0.513)	-3.28 (0.310)	-2.03 (0.437)	0.15(1.109)	< 0.001
Cases/controls (n)	253/252	251/250	255/251	248/251	0.997
Crude OR (95% CI)	1.00 ↓	1.00 (0.78–1.28)	1.01 (0.79–1.29)	0.98 (0.77–1.26)	0.997
Adjusted OR (95% CI) [a]	1.00 ↓	1.24 (0.93–1.65)	**1.57 (1.15–2.13)**	**1.56 (1.11–2.18)**	0.02
E-DII	< -2.8	-2.8 to < -1.71	-1.71 to < -0.42	-0.42 ≤	
DII score mean (S.D.)	-3.68 (0.692)	-2.21 (0.305)	-1.08 (0.358)	0.88 (1.033)	< 0.001
Cases/controls (n)	207/ 251	187/ 251	274/ 251	339/ 251	< 0.001
Crude OR (95% CIs)	1.00 ↓	0.90 (0.69–1.18)	**1.32 (1.03–1.70)**	**1.64 (1.28–2.09)**	< 0.001
Adjusted OR (95% CI) [b]	1.00 ↓	1.07 (0.80–1.43)	**1.47 (1.11–1.94)**	**1.87 (1.42–2.47)**	< 0.001
DII-s	< -5.05	-5.05 to < − 4.44	-4.44 to < -3.68	-3.68 ≤	
DII score mean (S.D.)	-5.54(0.391)	− 4.74 (0.175)	-4.10 (0.213)	-2.52 (1.225)	< 0.001
Cases/controls (n)	244 / 254	257 /250	250/249	256/251	0.95
Crude OR (95% CI)	1.00 ↓	1.07 (0.84–1.37)	1.05 (0.82–1.34)	1.06 (0.83–1.36)	0.95
Adjusted OR (95% CI) [c]	1.00 ↓	1.24 (0.94–1.65)	1.32 (0.99–1.76)	**1.43 (1.06–1.92)**	0.10
E-DII-s	< -4.58	-4.58 to < -3.77	-3.77 to < -2.87	-2.87 ≤	
DII score mean (S.D.)	-5.16 (0.457)	− 4.15 (0.231)	-3.36 (0.253)	-1.75 (1.181)	< 0.001
Cases/controls (n)	208/252	234/250	242/252	323/250	0.003

	Quartiles of DII and E-DII				
Crude OR (95% CI)	1.00 ↓	1.13 (0.88–1.47)	1.16 (0.90–1.50)	**1.57 (1.22–2.00)**	0.003
Adjusted OR (95% CI) [d]	1.00 ↓	1.34 (0.98–1.84)	1.34 (0.98–1.84)	**1.94 (1.42–2.65)**	0.001
DII: dietary inflammatory index, DII-s: DII including supplements, E-DII: energy-adjusted DII, E-DII-s: E-DII including supplements, n: number, Q: quartile and S.D.: standard deviation, OR: Odds ratio, CI: confidence intervals.					
↓ Reference category					
[a] Adjusted for the menopause status (pre-menopause and post-menopause), age at first pregnancy (unknown,< 25 and ≥ 25 years,), lactation number (unknown,< 2, 2 and ≥ 3), sum duration of breast feeding (unknown, < 24, 24 to < 48 and ≥ 48 month), average duration of each lactation(unknown < 18, 18 to < 24 and ≥ 24 month), type-2 diabetes (unknown, yes and no), BMI (< 25, 25 to < 30 and ≥ 30 kg/m^2), abortion history (unknown, yes and no) and energy (< 2074, 2074 to < 2697 and ≥ 2697 kcal/day).					
[b] Adjusted for the menopause status (pre-menopause and post-menopause), type-2 diabetes (unknown, yes and no), breast feeding history (unknown, yes and no), BMI (< 25, 25 to 30 and ≥ 30 kg/m^2), average duration of each lactation(unknown, < 18, 18 to < 24 and ≥ 24 month), sum duration of breast feeding (unknown < 24, 24 to < 48 and ≥ 48 month) and age at first pregnancy (unknown, < 25 and ≥ 25 years).					
[c] Adjusted for the menopause status (pre-menopause and post-menopause), type-2 diabetes (unknown, yes and no), BMI (< 25, 25 to < 30 and ≥ 30 kg/m^2), sum duration of breast feeding (unknown, < 24, 24 to < 48 and ≥ 48 month), age at first pregnancy (unknown, < 25 and ≥ 25 years), abortion history (unknown, yes and no,) and energy (< 2074, 2074 to < 2697 and ≥ 2697 kcal/day).					
[d] Adjusted for the menopause status (pre-menopause and post-menopause), age at first pregnancy (unknown,< 25 and ≥ 25 years), sum duration of breast feeding (unknown,< 24, 24 to < 48 and ≥ 48 month), average duration of each lactation(unknown,< 18, 18 to < 24 and ≥ 24 month), type-2 diabetes (unknown, yes and no) and BMI (< 25, 25 to < 30 and ≥ 30 kg/m^2).					

Figure 1 presents associations between E-DII (calculated both with and without supplements) and the risk of BrCa by taking into account the stratifications based on menopausal status. For multivariable-adjusted models, the findings showed that higher strata of E-DII were associated with an increased risk of BrCa only among premenopausal women (OR $_{Q3\ vs.\ Q1}$: 1.66; 95% CI: 1.20–2.31, OR $_{Q4\ vs.\ Q1}$: 2.32; 95% CI: 1.67–3.20; P $_{trend}$ < 0.001). The increasing trends of E-DII-s (including supplements) across strata were associated with elevated risk of BrCa; these were significant only among premenopausal women in the multivariable-adjusted analysis; i.e., after adjusting for potential confounders (OR $_{Q2\ vs.\ Q1}$: 1.44; 95% CI: 1.04–1.99, OR $_{Q3\ vs.\ Q1}$: 1.48; 95% CI: 1.07–2.04 and OR $_{Q4\ vs.\ Q1}$: 2.33; 95% CI: 1.70–3.21; P_{trend} < 0.001).

Table 3 presents the association of the overall anti-inflammatory (AI) potential of diet (i.e., E-DII scores < 0) compared to the overall pro-inflammatory diet (i.e., E-DII scores ≥ 0) with BrCa risk. The AI diet showed

a 37% decreased risk of BrCa vs. those who consumed a more pro-inflammatory diet (P < 0.001).

Table 3
Anti-inflammatory (i.e. E-DII < 0) and pro-inflammatory diets (i.e. E-DII ≥ 0) in association with BrCa risk.

E-DII scores	cases/controls (n)	OR	95% CI
Pro-inflammatory scores (≥ 0)	273/190	1.00	1.29–1.97
Anti-inflammatory scores (< 0)	734/814	0.63	0.51–0.77
E-DII: energy-adjusted DII, n: number, OR: Odds ratio, CI: confidence intervals. The estimated E-DII included zero (0) at all.			

Table 4 shows ORs and 95% CIs for the associations across quartiles of E-DII < 0 (the difference between series of quartiles = 1 unit) with BrCa risk when the E-DII ≥ 0 was considered as the reference category. Multivariate analysis showed that a one-unit decrease in E-DII score could significantly decreased BrCa risk ($OR_{Q4\ vs.\ pro-inflammatory\ category}$: 0.70; 95% CI: 0.53–0.91, $OR_{Q3\ vs.\ proinflammatory\ category}$: 0.69; 95% CI: 0.53–0.90; $OR_{Q2\ vs.\ proinflammatory\ category}$: 0.55; 95% CI: 0.42–0.73 and $OR_{Q1\ vs.\ proinflammatory\ category}$: 0.57; 95% CI: 0.44–0.76; P_{trend} < 0.001).

Table 4
Association between anti-inflammatory E-DII scores↓ compared to pro-inflammatory E-DII scores↓ and BrCa risk.

	Quartiles of E-DII					
	Q1	**Q2**	**Q3**	**Q4**	**PI E-DII**	**P-value for trend**
E-DII	< -3.0	-3.0 to < -2.0	-2 to < -1	-1 to < 0	≥ 0	
DII score mean (S.D.)	-3.86 (0.65)	-2.52 (0.29)	-1.60 (0.28)	-0.61 (0.32)	1.19 (0.97)	< 0.001
Cases/controls (n)	168/204	160/202	205/207	201/201	273/190	< 0.001
Crude OR (95% CI)	0.57 (0.44–0.76)	0.55 (0.42–0.73)	0.69 (0.53–0.90)	0.70 (0.53–0.91)	1.00↓↓	< 0.001
Adjusted OR (95% CI) [a]	0.52 (0.38–0.70)	0.56 (0.41–0.76)	0.71 (0.52–0.95)	0.72 (0.53–0.97)	1.00	< 0.001

E-DII: energy-adjusted DII, n: number, PI E-DII: pro-inflammatory E-DII, Q: quartile and S.D.: standard deviation, PI: pro-inflammatory, OR: Odds ratio, CI: confidence intervals.

↓ Anti-inflammatory E-DII scores are defined by E-DII-ES scores < 0. The pro-inflammatory E-DII scores are presentative of E-DII scores ≥ 0.

↓↓ Reference category.

[a] Adjusted for the age of menarche (unknown, < 13 and ≥ 13 years), sum duration of breast feeding (unknown, < 24, 24 to < 48 and ≥ 48 month), average duration of each lactation (unknown < 18, 18 to < 24 and ≥ 24 month), type-2 diabetes (unknown, yes and no) and BMI (< 25, 25 to < 30 and ≥ 30 kg/m^2).

DIIs, pathological features, and BrCa risk

The association between the inflammatory potential of diet and pathologic subtypes of BrCa is assessed in Supplementary Table 2. The results of the multivariable-adjusted models showed a positive association between E-DII and risk of IDC cases ($OR_{Q4\ vs.\ Q1}$: 1.81; 95% CI: 1.32–2.50; P_{trend} < 0.001) and ILCs ($OR_{Q4\ vs.\ Q1}$: 3.07; 95% CI: 1.34–7.02; P_{trend} = 0.07) in a case (pathologic subtype)–control design. The multivariable model indicated that E-DII-s was positively associated with increased risk of IDC cases ($OR_{Q4\ vs.\ Q1}$: 1.89; 95% CI: 1.35–2.63; P_{trend} = 0.002).

Figure 2 indicates the association between the inflammatory contents of diet in association with the HR status of BrCa. Crude analysis showed that the E-DII was positively associated with the higher risk

observed at HR^+ BrCa ($OR_{Q4\ vs.\ Q1}$: 1.58; 95% CI: 1.20–2.09; $P_{trend} < 0.001$). Higher E-DII-s scores were associated with increased risk of HR^+ BrCa ($OR_{Q4\ vs.\ Q1}$: 1.48; 95% CI: 1.12–1.96; $P_{trend} = 0.048$).

The pro-inflammatory diets in association with the risk of certain molecular subtypes of BrCa (luminal A, luminal B, HER2-enriched, and triple-negative) are summarized in Fig. 3. In the multivariable-adjusted models (Fig. 3b), E-DII was positively associated with the risk of BrCa expressing luminal A ($OR_{Q3\ vs.\ Q1}$: 1.50; 95% CI: 1.03–2.87, $OR_{Q4\ vs.\ Q1}$: 2.05; 95% CI: 1.42–2.95; $P_{trend} <0.001$), luminal B ($OR_{Q3\ vs.\ Q1}$: 1.80; 95% CI: 1.03–3.16, $OR_{Q4\ vs.\ Q1}$: 1.78; 95% CI: 1.00–3.16), and HER2-enriched BrCa ($OR_{Q4\ vs.\ Q1}$: 2.84; 95% CI: 1.3–6.16; $P_{trend} = 0.015$) via carrying out the case (molecular subtype)–control analyses. In the multivariate model (Fig. 3d), the highest strata of E-DII-s were associated with higher risks of luminal A incidence ($OR_{Q4\ vs.\ Q1}$: 1.98; 95% CI: 1.38–2.85; $P_{trend} = 0.002$) and even HER2-enriched subtypes ($OR_{Q4\ vs.\ Q1}$: 3.04; 95% CI: 1.45–6.39; $P_{trend} = 0.001$).

Figure 4 shows the DII across histological grades, different tumor size classifications, and molecular subtypes. DII scores increased significantly in was obtained in an ascending trend for with histological grades (P_{trend}=0.001, Fig. 4a). There were significant differences in mean DII between grade I and grade III ($P < 0.05$), and between grade II and grade III ($P < 0.05$). All forms of the DII (except DII, without supplements) was significantly associated with increasing tumor size (TSs) ($P < 0.05$; Fig. 3b). There were significant differences in mean DII, E-DII, and E-DII-s between TSs $\leq$ 2 cm and TSs > 5 cm ($P < 0.05$), and between 2 and $\leq$ 5 cm and TSs > 5 cm classifications ($P < 0.05$). No significant difference in DIIs was found between the molecular subtypes of BrCa (Fig. 4c).

The association between the E-DII and the risk of triple-negative subtype of BrCa compared to luminal A is indicated in Fig. 5a. The multivariate analysis showed that in patients who consumed a diet with higher inflammatory potential, the risk of having triple-negative disease was three times higher than the cases with luminal A ($OR_{Q4\ vs.\ Q1}$: 3.00; 95% CI: 1.002–8.96). The greater inflammatory potential of the diet increased the risk of HER2-enriched BrCa compared to luminal B in BrCa patients ($OR_{Q4\ vs.\ Q1}$: 2.44; 95% CI: 1.01–5.88; Fig. 5b).

Figure 6 illustrates the multivariate models showing positive correlations between E-DII and the risk of luminal A (Fig. 6b) ($OR_{Q3\ vs.\ Q1}$: 1.85; 95% CI: 1.18–2.91, $OR_{Q4\ vs.\ Q1}$: 2.71; 95% CI: 1.74–4.22; $P_{trend} <$ 0.001), luminal B (Fig. 6d) ($OR_{Q3\ vs.\ Q1}$: 2.37; 95% CI: 1.17–4.81, $OR_{Q4\ vs.\ Q1}$: 2.86; 95% CI: 1.39–5.89; $P_{trend} = 0.028$), and HER2-enriched (Fig. 6f) ($OR_{Q4\ vs.\ Q1}$: 2.86; 95% CI: 1.22–6.70; $P_{trend} = 0.006$) BrCa only in premenopausal women. It is important to note that in the postmenopausal women crude analysis showed a lower risk of luminal B BrCa in the second quartile (Fig. 6c) ($OR_{Q2\ vs.\ Q1}$: 0.25; 95% CI: 0.08–0.75), perhaps owing to AI scores being defined in certain ranges.

Discussion

This hospital-based, frequency-matched case–control study in Iran provides evidence to support a significant positive association between an increase in the inflammatory potential of diet and elevated risk of BrCa. The findings were most evident among premenopausal women, which calls into question the contribution of diet-associated inflammation to hormone-dependent inflammatory responses. We found that increasing the inflammatory potential of the diet was associated with greater risk of invasive subtypes of BrCa (triple-negative and HER2-enriched) compared to luminal A and luminal B BrCas. There was a positive association between the risk of developing HR-dependent molecular subtypes of BrCa (positive ER/PR vs. counterparts lacking ER/PR) in pre-menopause women, additionally emphasizing the interactions between HR and DII.

Previous meta-analyses/systematic reviews of observational studies have shown that women who tend to consume diets with higher inflammatory potential might also have a greater chance of developing BrCa (38, 39). Prospective studies also have documented the association between DII and BrCa risk (21, 22). Furthermore, follow-up data have confirmed the inflammatory effect of high DII diets in contributing to poor prognosis and overall poorer survival rates (40, 41). Consistently, large case-control studies in Italian (23) and Chinese women (24) showed that the DII was positively associated with the risk of BrCa. Nevertheless, some studies failed to achieve reasonable results for E-DII (13, 14). Therefore, this study's findings contribute to our understanding of how the inflammatory potential of diet influences BrCa risk.

The inconsistencies in the association between DII and BrCa in previous studies suggest heterogeneity of effects, indicating inter-individual variations in the effect of diet-associated inflammation or even the fact that in different situations different foods considered in the calculation of DII/E-DII may be exerting differential effects (13, 21–24, 40). It should be noted, however, that according to findings by Shivappa et al., the range of DII is more dependent on the amount of consumed food rather than the number of available food items (42). This is an important issue that we have discussed previously and which needs to be kept in mind as we designed and analyzed data from additional studies on this important subject (43)

It is important to note that the DII score estimated in our population represented more AI potencies of the Iranian diet (-2.43 ± 1.85) than the average of DII scores among other populations, such as Sweden (2.67 ± 1.47) (21), Germany (0.86 ± 1.30) (13), Italy (-1.05 ± 1.64) (44), America (-0.87 ± 2.02) (22), and China (-1.48 ± 1.78) (24). The relatively low DII/E-DII scores of this study population reflect the contents of the Iranian diet, proportionally consisting of large quantities of food items with anti-inflammatory effects, such as black tea, Persian saffron, onion (raw and cooked), garlic and plant-derived flavonoid contents (45–47). However, previous studies seem to have excluded food items in DII calculations comprised of AI contents (13, 21–24, 40).

Interestingly, the present study showed that the anti-inflammatory impacts of using supplements could mask the inflammatory potential of diets (DII-s and E-DII-s). Any supplements (trace elements and vitamins) can influence oxidative stress, proliferation rate and pro-apoptosis *in vitro* in addition to their inflammatory potencies (15, 48); and the anticancer effects of different supplements have been shown to

vary experimentally (49, 50). Currently, there is no consensus from epidemiologic studies regarding the benefits of supplement use in association with BrCa risk or improved survival rates. This is consistent with what it has been seen with single- or two-agent intervention trials using β-carotene, α-tocopherol and selenium to prevent lung and prostate cancer (51–53). The whole purpose of designing the DII was to avoid this kind of problem that results from a nutrient-specific focus (43). Regarding the effects of supplements on both inflammation and BrCa risk (6), it is imperative for future studies to consider collecting data on dietary supplements so that they can be part of DII calculations.

A meta-analysis of four prospective and three case–control studies also showed that DII can increase the risk of BrCa among premenopausal women but not among postmenopausal women (54). Current findings provided additional evidence suggesting positive associations between E-DII and BrCa risk, as a menopausal-dependent result. Significant findings in premenopausal women can highlight the possible impact of E2 presents during reproductive ages, to shed light upon E2 to synergize the inflammatory states supported by pro-inflammatory diets. Despite the hormone-dependent inflammatory responses (40), there is sufficient evidence to support the regulatory effects of cytokines on mediating the E2 synthesis (10, 37). Therefore, a synergistic relationship between E2 levels and inflammation (partly corresponding to DII) should not be ignored when considering the etiology of BrCa.

Some studies have shown that the inflammatory potential of diet could increase the risk of HR expressing BrCa subtype (24, 40). Jang et al. (40) demonstrated that pro-inflammatory DII score in association with increased risk of BrCa recurrence in HR^+ women. Consistently, Huang et al. (24) reported that the DII score could be positively associated with the incidence of ER^+ and PR^+ BrCa. Patients with ER^+ tumors may be responsive to adjuvant anti-hormone therapies, representing a better prognosis in contrast to ER^- or triple-negative tumors (55). Diets that have the potential to contribute to chronic, systemic inflammation is one that would lead to epigenetic reprogramming of ER^+ tumors and eventually might confer non-responsiveness to cancer endocrine-therapy (24, 40). Considering molecular disease subgroups has the potential to lead to advances in our understanding of diet-associated inflammation and increased risk of BrCa.

To the best of our knowledge, this study is the first to show that those BrCa patients who had higher E-DII scores appear to be at higher risk of more invasive BrCa phenotypes, for instance, triple-negative (vs. luminal A) and HER2-enriched (vs. luminal B) BrCas. A large cohort study demonstrated that the pro-inflammatory potential of a diet could be associated with an increased risk of developing breast tumors lacking ER and PR expressions despite having $HER2^+$ subtypes among postmenopausal women (56). In this context, Tabung et al. discovered that pro-inflammatory DII scores increased the risk of $HER2^+$ BrCa (41). Consistent with this evidence, a large population-based cross-sectional study demonstrated positive associations between the levels of circulating cytokines and the risk of tumors lacking the expression of ER and triple-negative phenotype vs. luminal A (57). From a mechanistic view, an *in vitro* experimental study supported the elevated expression levels of cyclooxygenase-2 (COX-2) in $HER2^+$ BrCa cell lines (58). Accordingly, COX-2 over-expression is seen in basal-like BrCa cell lines (SUM159PT and SUM149PT), and

even in breast cancer stem cells (59). Moreover, nuclear factor kappa-light-chain-enhancer of activated B cells activation, as a hallmark upstream transcriptional factor of cytokines, might contribute to the elevated risk of developing ER^- and $HER2^+$ subtypes of BrCa (60). The T helper-2-related cytokines are more likely to contribute to incorporating triple-negative pathogenesis among premenopausal women (57). This suggests a key role of oncologic inflammation in the development of triple-negative or HER2 expressing tumors (61).

Consistent with our findings, Jang et al. (40) showed that DII scores correlated with increase breast tumor sizes. The invasive pathologic circumstances could associate with the secretion of inflammatory cytokines (62). Tumor cells express TNF-α and IL-1B (62). It seems that tumor size is an indicator that might interpret the inflammatory-related pathologic progress (62). In addition, the pro-inflammatory diet can influence the serum levels of IL-6, IL-1β, TNF-α, or CRP (12, 42). Therefore, it seems essential to consider tumor size in investigations focusing on DII in association with BrCa risk.

Limitations of this study should be noted. There is a potential for information bias, which may be inherent in case-control study designs that have to rely on the retrospective assessment of lifestyle behaviors and other factors. In addition, selection bias also may also plague studies of case-control design (63). Despite its limitations, the study has several strengths. First is its large sample size. Second, it used a validated 136-item FFQ that provided a much higher than average (i.e., 39 out of 45) food parameters to calculate DII scores.

Conclusions

In conclusion, results from this study showed that the tendency to consume a pro-inflammatory diet could be associated with an increased risk of BrCa, especially in premenopausal women and patients with HR^+ phenotypes of BrCa, and there could be a connection between estrogen-related signaling and inflammation in association with this cancer risk. The elevated inflammatory potential of diet might be associated with aggressive BrCa phenotypes. Increases in dietary inflammatory scores showed a positive association with advanced pathological phenotypes (tumor size > 2.0 cm and tumor grade > 2), which might be connected to the prognosis of BrCa.

List Of Abbreviations

ANOVA, analysis of variance; ANCOVA, analysis of covariance; BrCa, breast cancer; BMI, body mass index; CRP, C-reactive protein; CI, confidence interval; DII, dietary inflammatory index; DII-s, DII including supplements; E-DII, energy-adjusted DII; E-DII-s, E-DII including supplements; E2, estradiol; ER, estrogen receptor; FFQ, food frequency questionnaire; HER2-neu, human epidermal growth factor receptor 2; HSD17β, 17β-hydroxysteroid dehydrogenase; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10; OR, odds ratio; PR, progesterone receptor; TS, tumor size; TNF-α, tumor necrosis factor-α.

Declarations

Ethics approval and consent to participate

The design and procedural steps of the study were carried out according to ethical standards of Helsinki Declaration. The research methodology and related ethical considerations were reviewed and approved by the Ethics Committee of Tabriz University of Medical Sciences under the code IR.TBZMED.REC.1396.763. Informed consent was obtained from all individual participants prior to their enrolment in the study.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Tabriz University of Medical Sciences (TUMS) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of TUMS.

Competing interests

The authors declare that they have no competing interests. Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed 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. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This is a part of the M.Sc. degree thesis entitled "Association between dietary inflammatory index and breast cancer risk: a case-control study based on hospital data “with registration no: 5-D-593903 approved by Faculty of Nutrition and Food Sciences, Tabriz University of Medical Science.

Authors' contributions

S.P., Z.H., and V.M. contributed to the conception of the study, design, data collections, statistical analysis, data interpretation, and drafting of this manuscript.

N.S., and J R. H. contributed to the statistical analysis, data interpretation, and drafting of this manuscript. S.P. supervised the study. All authors read and approved the final manuscript prior to submission.

Acknowledgments

The authors are grateful for the great contribution of study participants since without their generous help the study would not have been possible. We are also grateful for the support given by our colleagues in Noor-Nejat hospital, Shams hospital, Shahid Ghazi Educational-Oncology hospital and several oncology clinics located in Tabriz.

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Figures

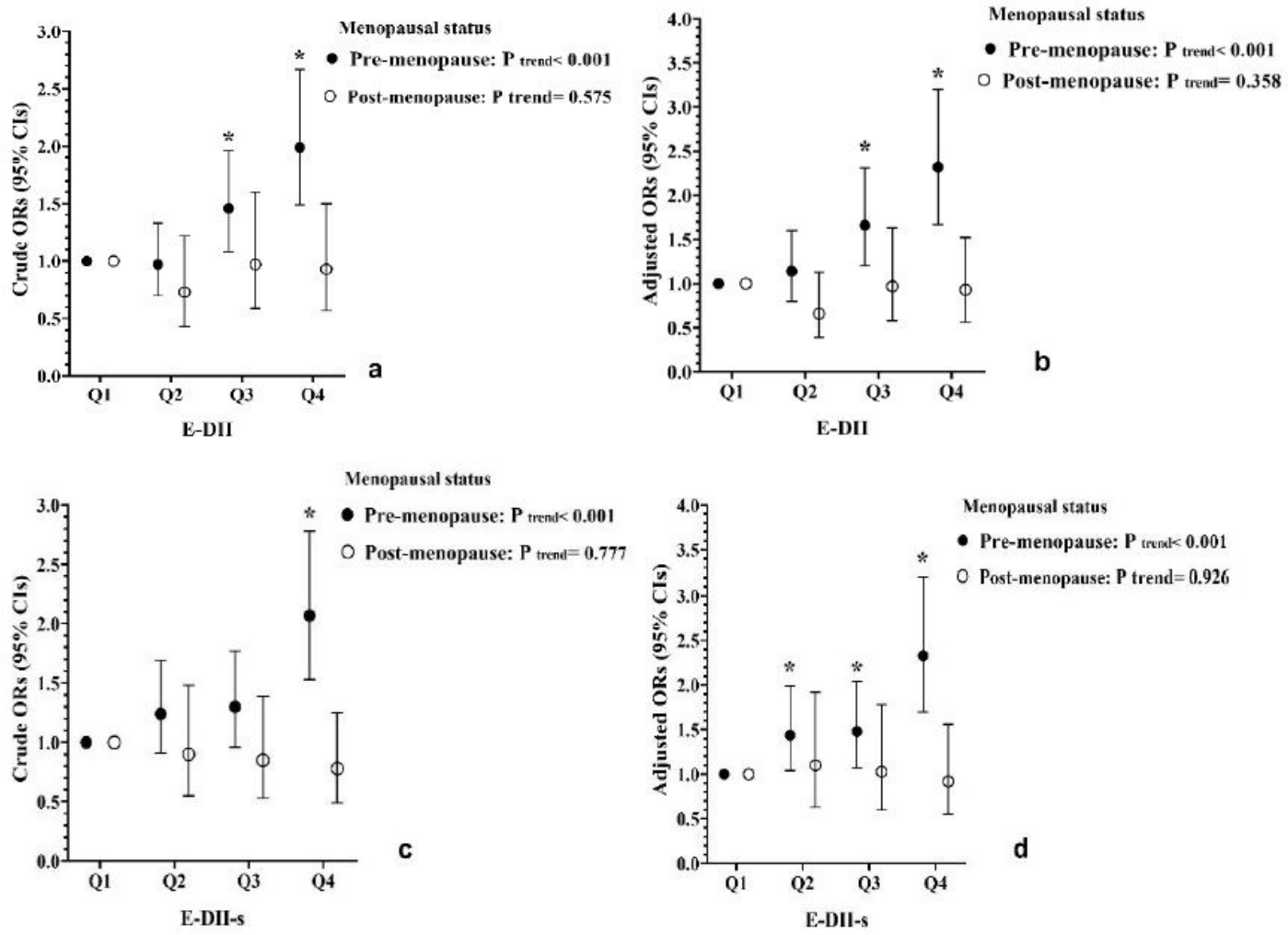

Figure 1

Association between E-DII (with and without supplements) and BrCa risk in different menopausal status. Crude odds ratio (ORs) and 95% confidence intervals (CIs) for the for BrCa risk among premenopausal and postmenopausal subjects are shown according to quartiles of E-DII (panel a) and E-DII-s (panel c). Multivariate models were created as follow: Panel b; Premenopausal status: Adjustments were made for the age at first pregnancy (unknown, <25 and ≥25 years), sum duration of breastfeeding (unknown, <24, 24 to <48, and ≥48 months), type 2 diabetes (unknown, yes and no) and BMI (<25, 25 to <30, and ≥30 kg/m2). Postmenopausal status: Adjustments were made for the age at menarche (unknown, < 13 and ≥ 13), type-2 diabetes (unknown, yes and no), and BMI (< 25, 25 to <30, and ≥30 kg/m2). Panel d; Premenopausal status: Adjustments were performed for the age at first pregnancy (unknown, <25 and ≥25 years), abortion history (unknown, yes and no), pregnancy number (unknown, <2, 2, and ≥3), type 2 diabetes (unknown, yes and no), and BMI (<25, 25 to <30, and ≥30 kg/m2). Postmenopausal status: Adjustments were made for the breastfeeding history (unknown, yes and no), type 2 diabetes (unknown, yes and no), the average duration of lactation (unknown, <18, 18 to <24, and ≥24 months) and BMI (<25, 25 to <30, and ≥30 kg/m2). *P<0.05 indicated significant difference vs. Q1. DII: dietary inflammatory

index (i.e., DII excluding supplements); E-DII: energy-adjusted DII; DII-s: DII including supplements; E-DII-s: E-DII including supplements; and Q: quartile.

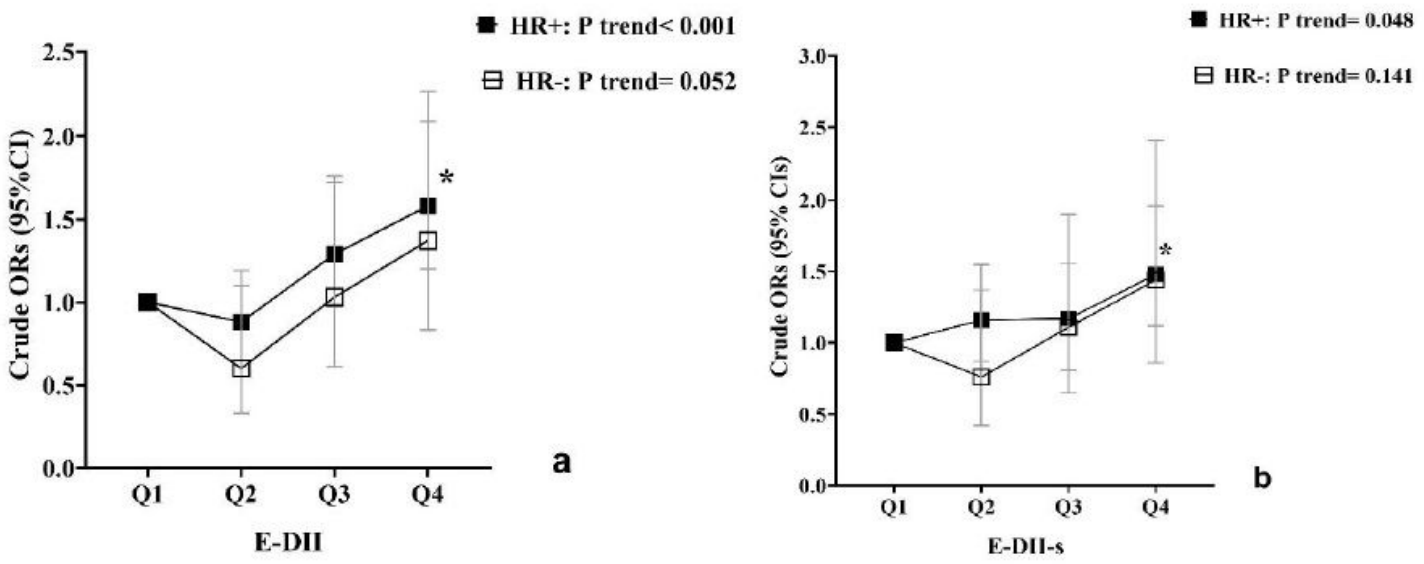

Figure 2

The risk of hormone receptor-related BrCa vs. controls, according to E-DII (a) and E-DII-s (b) status. *P<0.05 indicated significant difference vs. Q1. HR: hormone receptor; E-DII: energy-adjusted dietary inflammatory index; E-DII-s: E-DII including supplements and Q: quartile, OR: odds ratio, CI: confidence interval.

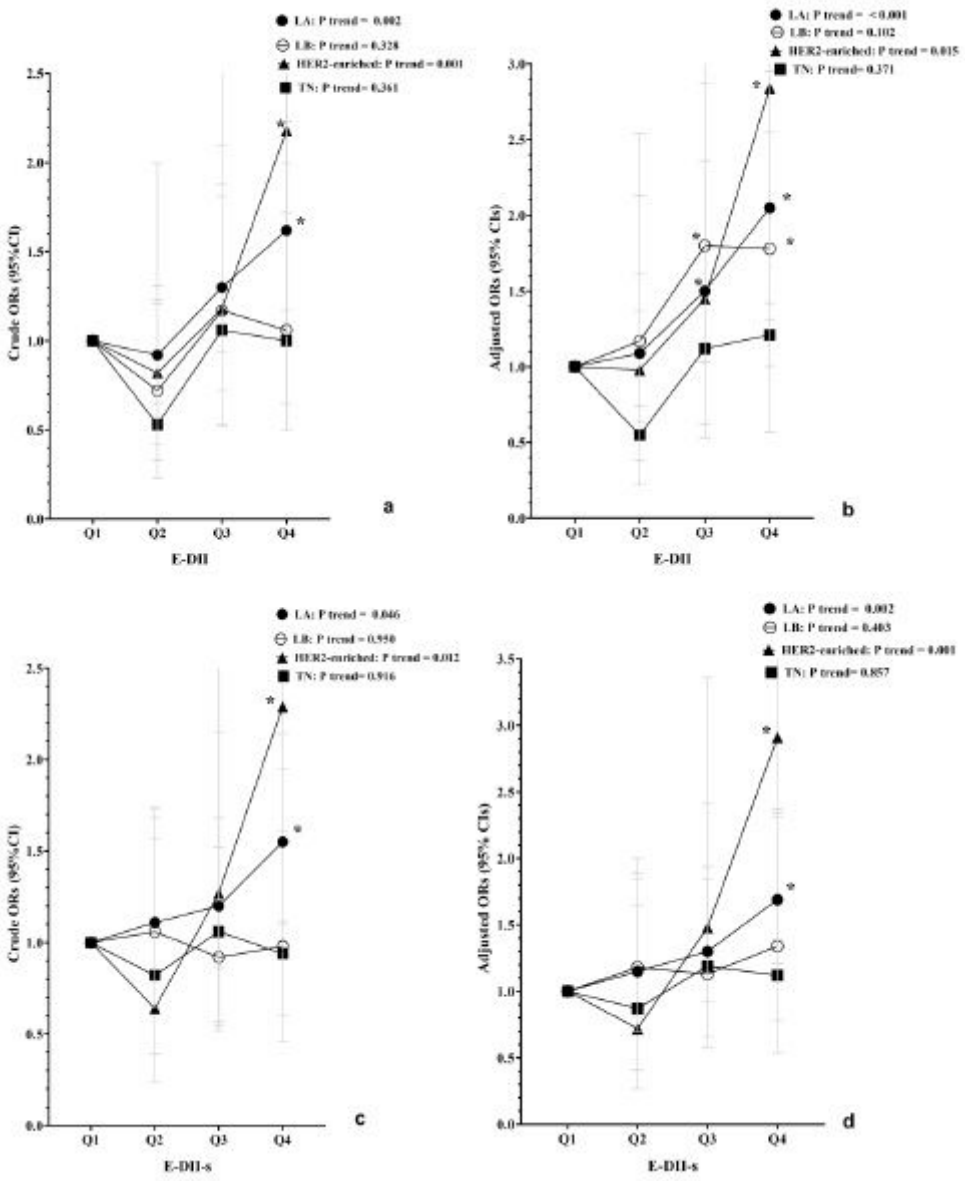

Figure 3

The risk of molecular subtypes of BrCa in association with E-DII status. Crude odds ratio (ORs) and 95% confidence intervals (CIs) for the risk of BrCa molecular subtypes, including (luminal A, luminal B, HER2-enriched and triple-negative) vs. control group were shown according to quartiles of E-DII (Panel a) and E-DII-s (Panel c). Multivariate models were created as follow: Panel b; Luminal A: adjustments were performed for the age at first pregnancy (unknown, <25 and ≥25 years), the average duration of each lactation (unknown, <18, 18 to <24, and ≥24 months) and BMI (<25, 25 to <30, and ≥30 kg/m2). Luminal B: Adjustments were made for the abortion history (unknown, yes and no), pregnancy number (unknown, <2, 2, and ≥3), sum duration of breastfeeding (unknown, <24, 24 to <48, ≥48 months) and BMI (<25, 25 to < 30, and ≥30 kg/m2). HER2-enriched: adjustments were performed for the age at first pregnancy (unknown, <25, and ≥25 years) and average duration of each lactation (unknown, <18, 18 to <24, and ≥24 months). Triple-negative: Adjustments were made for the sum duration of breastfeeding (unknown,

<24, 24 to <48, and ≥48 months). Panel d; Luminal A: adjustments were performed for the sum duration of breastfeeding (unknown, <24, 24 to <48, and ≥48 months) and BMI (<25, 25 to <30, and ≥30 kg/m2). Luminal B: adjustments were performed for the age at first pregnancy (unknown, < 25, and ≥25 years), sum duration of breastfeeding (unknown, <24, 24 to <48, and ≥48 months) and abortion history (unknown, yes, and no). HER2-enriched: adjustments were performed for the average duration of each lactation (unknown, <18, 18 to <24, and ≥24 months). Triple-negative: Adjustments were made for the sum duration of breastfeeding (unknown, <24, 24 to <48, and ≥48 months). *P<0.05 indicated significant difference vs. Q1. E-DII: energy-adjusted dietary inflammatory index; (i.e., E-DII excluding supplements; E-DII-s: E-DII including supplements; LA: luminal A; LB: luminal B; HER2-enriched: human epidermal growth factor receptor 2- enriched; TN: triple-negative; and Q: quartile.

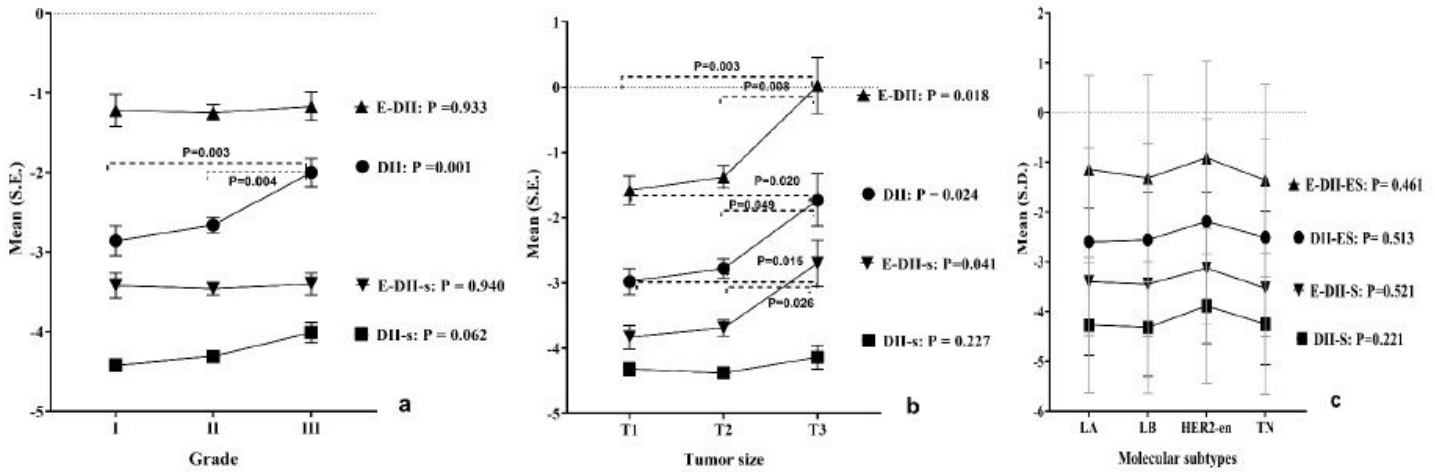

Figure 4

Comparing DII scores among histological grades, different classifications of tumor size and molecular subtypes of BrCa. Panel a; represents the results of ANOVA. Panel b; represents the results of ANCOVA. The DII was adjusted for covariates, including age at menopause (≤45 and >45 years), age at menarche (unknown, <13, and ≥13), energy (<2074, 2074 to <2697, and ≥2697 kcal/day) and BMI (<25, 25 to <30, and ≥30 kg/m2). The DII-S was adjusted for the age at menarche (unknown, <13, and ≥13), BMI (<25, 25 to <30, and ≥30 kg/m2) and waist-to-hip ratio (<85 and ≥85). The E-DII was adjusted for the age at menopause (≤45 and >45 years), age at menarche (unknown, <13, and ≥13) and BMI (<25, 25 to <30, and ≥30 kg/m2). The E-DII-s was adjusted for the age at menopause (≤45 and >45 years), age at menarche (unknown, <13, and ≥13), lactation number (unknown, <2, 2, and ≥3) and pregnancy number (unknown, <2, 2, and ≥3). Panel C; represents the results of ANOVA. DII: dietary inflammatory index; E-DII: energy-adjusted DII; DII-s: DII including supplements; E-DII-s: E-DII including supplements, LA: luminal A, LB: luminal B, HER2-en: human epidermal growth factor receptor 2-enriched; TN: triple-negative; ANOVA: analysis of variances; SD: standard deviation; and S.E.: standard error.

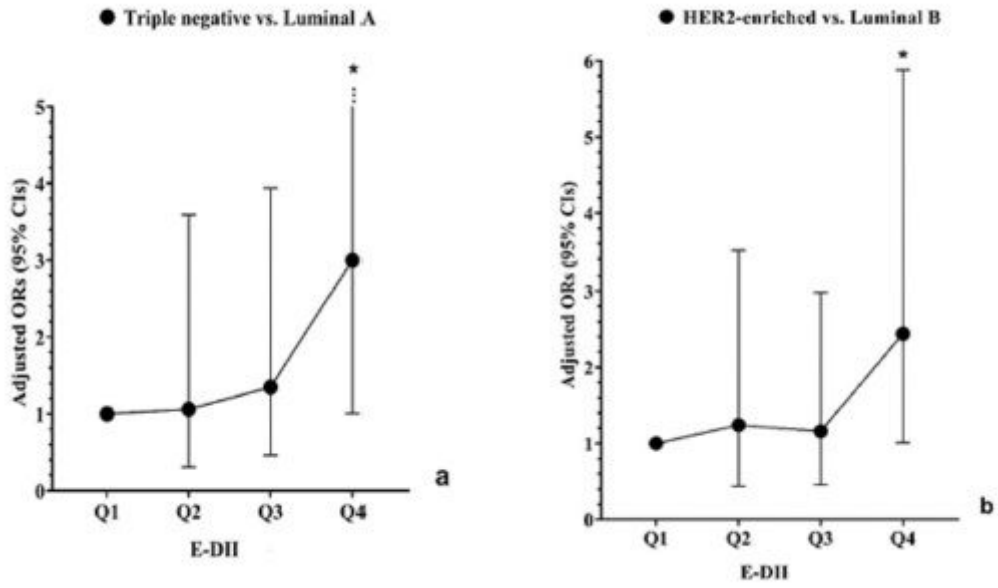

Figure 5

Risk of triple-negative (vs. luminal A) and HER2-enriched BrCa (vs. luminal B) related to E-DII status. Panel a: Adjustments were made for the abortion history (unknown, yes, and no), oral contraceptive use (unknown, yes, and no), height-to-wrist circumference ratio (<10.1, 10.1 to <11, and ≥11), x-ray exposure (unknown, yes, and no), anti-lipid consumption (yes and no), and energy (<2074, 2074 to <2697, and ≥2697 kcal/day). Panel b: Adjustments were made for the oral contraceptive use (unknown, yes, and no), age at first pregnancy (unknown, <25 and ≥25 years), pregnancy number (<2, 2, and ≥3), type 2 diabetes (unknown, yes, and no), and first-degree family history of BrCa (unknown, yes and no). *P<0.05 indicated significant difference vs. Q1. E-DII: energy-adjusted dietary inflammatory index; E-DII-s: E-DII including supplements; HER2-enriched: human epidermal growth factor receptor 2-enriched; and Q: quartile, OR: odds ratio, CI: confidence interval.

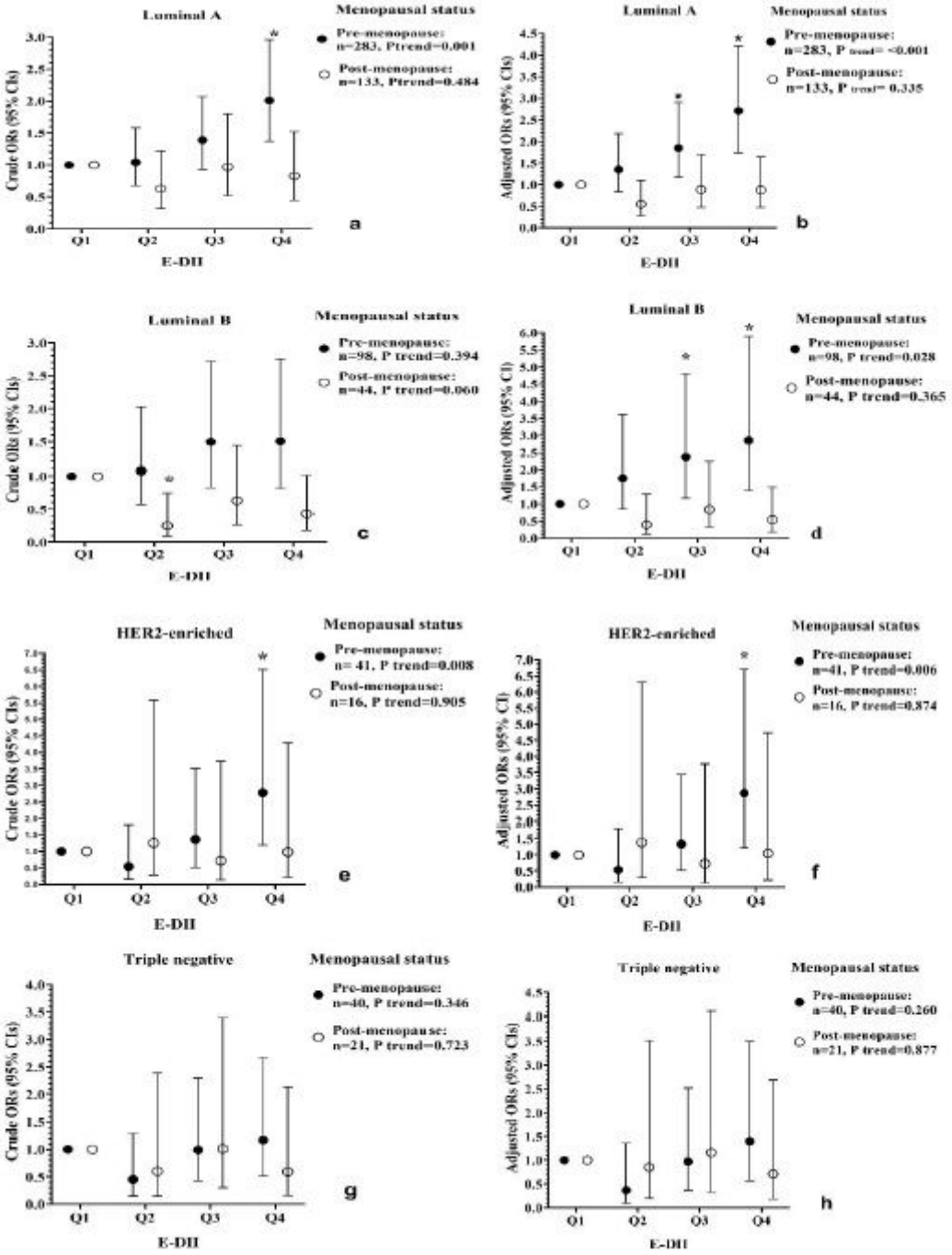

Figure 6

Risk of molecular subtypes of BrCa according to menopausal status related to E-DII quartiles. Crude ORs and 95% CIs for risk of luminal A (Panel a), luminal B (Panel c), HER2-enriched (Panel e), and triple-negative (Panel g) molecular subtypes of BrCa in the menopausal status were shown according to quartiles of E-DII. Multivariate models were created as follow: Panel b; Pre-menopause status: Adjustments were performed for the sum duration of breastfeeding (unknown, <24, 24 to <48, and ≥48 months), abortion history (unknown, yes, and no) and BMI (<25, 25 to <30, and ≥30 kg/m2) Post-menopause status: Adjustments were made for the age at first pregnancy (unknown, <25, and ≥ 25

years) and BMI (<25, 25 to <30, and ≥30 kg/m2). Panel d; Pre-menopause status: Adjustments were made for the sum duration of breastfeeding (unknown, <24, 24 to <48, and ≥48 months), abortion history (unknown, yes, and no), and BMI (<25, 25 to <30, and ≥30 kg/m2). Post-menopause status: Adjustments were made for the sum duration of breastfeeding (unknown, <24, 24 to <48, and ≥48 months), average duration of each lactation (unknown, <18, 18 to <24, ≥24 month) and BMI (<25, 25 to <30, and ≥30 kg/m2). Panel f; Pre-menopause status: Adjustments were made for the pregnancy number (unknown, <2, 2, and ≥3). Post-menopause status: Adjustments were made for abortion history (unknown, yes, and no). Panel h; Pre-menopause status: Adjustments were made for the average duration of each lactation (unknown, <18, 18 to <24, ≥24 months). Post-menopause status: Adjustments were made for the average duration of each lactation (unknown, < 18, 18 to <24, ≥24 months). *P<0.05 indicated significant difference vs. Q1. E-DII: energy-adjusted dietary inflammatory index; E-DII-s: E-DII including supplements; n: number; and Q: quartile, OR: odds ratio, CI: confidence interval.

Supplementary Files

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- Additionalfile1.docx
- Additionalfile2.docx