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Dietary Patterns and Risk of Breast Cancer among Pre and Post-Menopausal Women: A Case-Control Study in Iran

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ABSTRACT

Background: Most of previous studies have investigated the association of specific food or nutrient with risk of breast cancer (BC) rather than overall diet and there is lack of evidence regarding dietary pattern in BC development. This study aims to examine the association between dietary patterns and risk of BC among Iranian women. **Methods:** This case–control study was carried out on 453 BC women and 496 healthy controls. A reliable and valid FFQ was used to evaluate usual dietary intake. Factor analysis was also applied to address the most major dietary patterns which were known as the healthy and unhealthy dietary patterns. **Results:** Those in the highest quartile of healthy dietary pattern had lower risk of BC (P = 0.001). However, being in the highest quartile of unhealthy pattern was associated with 2.04-fold increase of BC risk (P = 0.004) compared to the lowest quartile. In premenopausal women, risk of BC in upper quartile of healthy pattern was lower than the lowest quartile (OR = 0.47; CI = 0.26 – 0.83, P = 0.004). More adherence to the unhealthy dietary pattern was associated with higher risk of BC (OR = 2.85; 95% CI = 1.57- 5.17, P < 0.0001). No significant association was observed between the healthy or unhealthy dietary patterns among postmenopausal women. **Conclusion:** The findings indicated that the healthy dietary pattern could be considered as a protective factor in terms of BC in women and particularly among premenopausal women.

Keywords: *Dietary pattern; Breast neoplasms; Factor analysis; Case-control*

Introduction

Breast cancer (BC) is the most common cancer among women all over the world (Fitzmaurice *et al.*, 2017). Although incidence rate of BC is much more in western countries than Asian countries, its

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rate is increasing in Middle-eastern countries, including Iran (Althuis *et al.*, 2005, Pisani *et al.*, 2002, Rouhollahi *et al.*, 2014, Youlden *et al.*, 2014). In 2018, the incidence of BC was 31 per 100000 in Iranian women (International Agency for Research on Cancer (IARC), 2018, Zendehdel, 2019). High burden of BC has directed many investigations to design and imply prevention strategies by knowing more about its risk factors (Daroudi *et al.*, 2015).

BC is a multifactorial disease and is related to genetic, age, obesity, and several other factors (Ghiasvand *et al.*, 2012). However, among the mentioned factors, diet is a modifiable risk factor that has been studied in several previous investigations (Lima *et al.*, 2008, Michels *et al.*, 2007, Seiler *et al.*, 2018). The increasing trend of the incidence of BC among Asian immigrants in western countries (Althuis *et al.*, 2005, Gomez *et al.*, 2017, Shuldiner *et al.*, 2018, Wu and Bernstein, 1998) suggests that environmental factors have an essential role in BC incidence (Hiatt and Brody, 2018). Several studies have shown the association between BC risk and dietary factors. However, controversial findings have been reported (Farvid *et al.*, 2014, Farvid *et al.*, 2018a, Kim *et al.*, 2016). These studies have not considered the interaction between various components of diet (Farvid *et al.*, 2018b, Genkinger *et al.*, 2012). It could be important for public health programs because people do not intake separated nutrients or foods. These interactions could be captured when all foods of diet are evaluated entirety. Therefore, assessment of dietary patterns could add information about BC risk factors (Link *et al.*, 2013).

Several studies have assessed the association between dietary pattern and BC in developed countries and found an increased risk of BC in individuals who followed "western dietary pattern" (Agurs-Collins *et al.*, 2009, Buck *et al.*, 2011). A study in Shanghai conducted on BC showed similar results in this regard (Cui *et al.*, 2007). In China, vegetable-fruit-soy-milk-fish pattern was a protective factor, while refined grain-meat-pickle pattern was demonstrated as a risk factor of BC (Zhang *et al.*, 2011). A study from Japan showed three dietary patterns, including vegetable pattern, animal food pattern, and dairy product pattern (Kojima *et al.*, 2017). In contrast to previous studies (Guo *et al.*, 2015, Inoue-Choi *et al.*, 2016), animal food pattern significantly decreased the risk of BC in the mentioned Japanese study (Kojima *et al.*, 2017). However, some studies reported null relations regarding different dietary patterns and BC (Buck *et al.*, 2011, Couto *et al.*, 2013). In Iran, a case-control study on 274 BC patients illustrated that those who followed "unhealthy" dietary pattern had higher risk of BC (Karimi *et al.*, 2014).

Middle-eastern region is a unique place for nutrition epidemiology studies due to the variety of dietary patterns and also high intake of refined carbohydrates and hydrogenated fats. Moreover, nutrition transition is taking place in this region (Esmaillzadeh and Azadbakht, 2008, Mazzocchi *et al.*, 2008). Dietary pattern changes and non-communicable diseases are related in the region (Hawkes, 2006). Hence, Iranian dietary patterns should be evaluated in terms of BC risk. In this study, the association between dietary patterns and the risk of BC among Iranian women is evaluated.

Materials and Methods

Participants: A hospital based case-control study was conducted during 2014-2016. The participants were women in the age range of 19-80 years who were admitted in the Cancer Institute of Iran (Atefeh Ardestani *et al.*, 2017). They were not on a specific diet. Moreover, 486 pathologically confirmed BC patients were recruited from surgery, chemotherapy or radiotherapy departments diagnosed within the previous year. They had no history of any cancers and were free of any diseases. The researchers recruited 523 controls frequency matched for age (10 year intervals), and residential place from healthy visitors, including visitors, relatives, and friends of non-cancer patients who were hospitalized for other chronic diseases in the hospital (a general hospital where cancer institute is situated in it).

For data analysis, the participants with a total energy intake of >5500 or <800 kcal/d, were excluded as under and over reporting (n = 35) (Vahid *et al.*, 2018). This value was also checked with the range of ±3SD energy intakes of all participants. However, if less than 70 items were answered and could not be completed through calling, the participant would be omitted (n=25). Finally, sixty participants were excluded and 453 cases and 496 controls were analyzed.

Assessment of dietary intake: All the participants completed a general questionnaire through a face to face interview. The questionnaire covered information about demographic and anthropometric characteristics, physical activity, and history of obstetrics and gynecology. Weight was measured while the women were without shoes and minimally clothed with using digital scales to the nearest 100g. Height was measured while the women were standing and without shoes by using tape meter. Body mass index (BMI) was calculated by dividing weigh by height squared. Global Physical Activity Questionnaire (GPAQ) was used to assess level of physical activity. GPAQ consists of 16 questions which are in 4 physical activity domains, including job related activities, transportation activities, recreation and sport activities, and sedentary behaviors. GPAQ Analysis Guide was applied to calculate MET-hours per week values (World Health Organization, 2012).

Dietary intake in the last year of date of the interview was estimated using a 168 item semi-quantitative Food Frequency Questionnaire (FFQ) administered by trained interviewers. Its validity was confirmed in Iranian society against urine potassium and nitrogen level as a gold standard for potassium and protein intake and double labeled water as a gold standard for energy intake (Mirmiran *et al.*, 2010). Moreover, it showed a good validity against 12 dietary recalls (Asghari *et al.*, 2012). The reliability was high when it was repeated one year later (Esfahani *et al.*, 2010). The data were converted to gram per day of food intake. Then, daily intake of energy and nutrients were computed using USDA food composition table (Gebhardt *et al.*, 2006).

Ethical considerations: The study was approved by ethics committee of Tehran University of Medical Science (Cod: 93-03-51-27113). An informed written consent was given from all the participants before interviewing.

Sample size and data analysis: Sample size was calculated based on the odds ratio (OR=1.5), prevalence of healthy diet (P = 25%), study power (β = 0.8) and level of significance (α = 0.05). The Number of participants for each group was estimated n = 466; however, regarding attrition in sample size we designed to recruit at least 500 cases and 500 controls. A factor analysis was performed with orthogonal rotations transformation on 42 food groups (**Appendix 1**) to extract major dietary patterns and retained factors in connection with Eigen values >1. It was performed on these 42 food groups based on the study outcome (cancer) and previous publications (Esmaillzadeh and Azadbakht, 2008, Esmaillzadeh *et al.*, 2007, Karimi *et al.*, 2014).The extracted factors (dietary patterns) were labeled on the basis of the interpretation from the study data and prior studies. Then, factor scores were calculated for each dietary pattern by summing intakes of food groups weighted by their factor loading. Each individual received a factor score for each identified pattern. Scores were adjusted for energy by using the residual method.

The participants were categorized into quartiles based on dietary pattern scores. One-way ANOVA and chi-square tests were used to compare distribution of continuous and categorical variables across dietary quartiles. Logistic regression was also utilized to assess the association of dietary patterns and the risk of BC by reporting odds ratio and 95% confidence interval.

Three main covariate-adjusted models were considered. The first model was adjusted for age, energy, family history of BC, BMI (continuously), menarche age, weight at age 18-20 y, and menopausal status (premenopausal or postmenopausal). Marital status was also added, parity in the 2nd model as a covariate. Additionally, in the 3rd model effect of couple of variables, including alcohol intake, menopausal hormone use, contraceptive use, and cigarette smoking, were also controlled as the confounders. Sub-group analysis was also done and all analyses were repeated for pre

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and post menopause women separately. All analysis was performed by Stata version 14 (State Corp, College Station, TX).

Results

Two main dietary patterns were identified from this study (**Appendix 2**). These patterns included the healthy dietary pattern (high intake of fruits, fruit juices, cruciferous vegetables, yellow vegetables, tomatoes, green leafy vegetables, other vegetables, and garlic), and the unhealthy dietary pattern (high intake of processed meat, eggs, butter, refined grains, mayonnaise, hydrogenated fat, sugars, soft drinks, and pickles). These labels were chosen based on the dietary pattern labels in previous studies (Esmaillzadeh and Azadbakht, 2008, Esmaillzadeh *et al.*, 2007, Karimi *et al.*, 2014). These two dietary patterns explained 71.9% of the whole variance and 47.9 and 23.9% for healthy dietary pattern and unhealthy dietary pattern, respectively.

Demographic, reproductive, and lifestyle characteristics of the subjects of case and control groups are provided in **Table 1**. BC patients were slightly older (P = 0.002), had lower BMI (P = 0.02), and have more family history of BC (P < 0.001) compared to the control group. The patients had lower physical activity (P < 0.001), were less married (P = 0.001), had lower rate of consumption of oral contraceptives (P = 0.02), had lower rate of using postmenopausal hormones (P = 0.03) and were less alcohol users (P = 0.01) compared to the control group. The patients had lower intakes of vegetables compared to the control group.

Table 2 shows the participants' characteristics across quartiles of the addressed dietary patterns. The highest mean age was observed in the fourth quartile healthy dietary pattern (47.7 ± 10.2 years); while in unhealthy dietary pattern the first quartile had the highest mean age (49.1 ± 9.6 years). Women in the top quartile of the healthy dietary pattern score had more slightly higher BMI, higher age at menarche, more percentage of menopause women, and more number of children compared to those in the lowest quartile of the healthy dietary pattern. Significant differences were found for physical activity level across quartile of healthy dietary pattern (P < 0.0001). Compared with those in the lowest quartile, the subjects in the upper quartile of healthy dietary pattern consumed more carbohydrate (P = 0.04). Individuals with greater unhealthy dietary pattern score had lower BMI, later menarche, lower percentage of menopause women, more nulliparous/missing, and low number of children compared to those in the lowest quartile. Higher intakes of carbohydrate and lower intakes of protein and fat were found among the subjects in top quartile of unhealthy dietary pattern.

Odds ratios of BC across categories of each dietary pattern score are presented in **Table 3**. The odds ratios of before and after multivariable adjustment for age and energy have shown significant association between the two major dietary pattern and BC. It is observed that healthy dietary pattern could decrease risk of BC (OR = 0.61; 95% CI = 0.41-0.92, P = 0.008) in model 1. In contrast, the unhealthy pattern was in relation to an increase of BC (OR = 1.82; 95% CI=1.20-2.76, P = 0.001). Comparing to the lowest quartile, risk of BC was decreased by 43% in the highest quartile of healthy dietary pattern (P = 0.003); whereas according to model 2, the highest quartile of unhealthy pattern had 1.87-fold increase of BC risk (OR = 1.87; 95% CI = 1.23-2.86, P = 0.001) compared to the lowest quartile. After additional adjustment for all confounders in model 3, negative association was addressed between the healthy pattern score and risk of BC (OR = 0.52; 95% CI = 0.33-0.82, P = 0.001) while a positive association was found between score of unhealthy pattern and risk of BC (OR = 1.96; 95% CI = 1.23-3.10, P = 0.004).

Table 4 provides the relationship between each dietary pattern and risk of BC for pre-and postmenopausal women. In premenopausal women, there is a negative association between risk of BC and score of healthy dietary pattern. Odds ratio for BC decreased by increasing the score of healthy pattern (OR= 0.52; 95% CI = 0.31-0.87, P = 0.008) in model 1. In contrast, premenopausal women in upper quartile of unhealthy pattern increased risk of BC compare to the lowest quartile (OR = 2.55; CI =

1.48-4.40, *P* < 0.0001). After controlling for further confounders, these associations remained significant in model 2. Additional adjustment for premenopausal showed that healthy pattern had 53% decrease in BC risk (*P* = 0.004), while unhealthy pattern had 2.85-fold increase in BC risk (*P* < 0.0001). In the postmenopausal women, no significant association was observed between the healthy or unhealthy dietary pattern

Table 1. Baseline demographic and daily dietary intake in termr of case and control.

Variables	Case (n = 453)	Control (n = 496)	P-value[a]
Age (y)	46.0 ± 10.3[b]	44.0 ± 11.2	0.002
Body mass index (kg/m^2)	28.1 ± 5.1	28.8 ± 6.0	0.02
Physical activity (MET h/wk)	20.0 ± 24.8	27.1 ± 38.8	<0.001
Age (y)	12.9 ± 2.8	12.9 ± 2.7	0.47
Whole grains (g)	98.4 ± 4.9	98.4 ± 5.2	0.49
Refined grains (g)	338.3 ± 9.4	318.5 ± 8.4	0.05
Fruits (g)	581.8 ± 18.7	595.8 ± 17.8	0.29
Vegetables (g)	358.9 ± 11.8	385.0 ± 10.5	0.05
Legumes (g)	38.8 ± 1.9	42.6 ± 2.9	0.15
Red meat (g)	14.6 ± 0.8	16.4 ± 0.9	0.08
Energy (kcal)	2783.0 ± 48.5	2720.5 ± 47.8	0.17
Carbohydrate (g)	346.8 ± 6.4	340.8 ± 6.4	0.25
Protein (g)	80.6 ± 1.5	82.5 ± 1.7	0.21
Fat (g)	125.7 ± 3.3	120.5 ± 3.1	0.12
Fiber (g)	23.0 ± 0.5	23.5 ± 0.5	0.23
Educational level			
Non-University	377 (83.7)[c]	408 (84.1)	0.27
University	73 (16.2)	77 (15.8)	
Marital status			
Married	368 (81.2)	417 (84.0)	0.001
Unmarried/divorced/widowed	85 (18.7)	79 (15.9)	
Menopausal status			
Premenopausal	301 (48.1)	324 (51.8)	0.97
Postmenopausal	152 (48.2)	163 (51.7)	
Family history of breast cancer BC (yes)	44 (9.7)	7 (1.4)	<0.001
Oral contraceptive use (yes)	214 (52.3)	258 (60.9)	0.02
Postmenopausal hormone use	2 (0.4)	10 (2.0)	0.03
Current smoking	17 (3.7)	24 (4.9)	0.27
Alcohol intake	12 (2.6)	30 (6.1)	0.01
Fertility treatment	19 (4.5)	10 (6.1)	0.29
Parity			
Nulliparous/missing	196 (43.2)	210 (42.3)	0.82
1	39 (8.6)	51 (10.2)	
2-3	147 (32.4)	155 (31.2)	
≥4	71 (16.6)	80 (16.1)	

[a]: χ^2 Test for ordinal qualitative variables and t-test for continuous variable; [b]: Mean ± SD ; [c]: N(%).

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Table 2. Characteristics and daily dietary intake of the study population by quartile (Q) categories of dietary patterns scores .

Variables	Quartile of "healthy" dietary pattern score					Quartile of "unhealthy" dietary pattern score				
	Q1	Q2	Q3	Q4	P-trend[a]	Q1	Q2	Q3	Q4	P-trend
Case/control	124/104	113/114	90/138	103/124		106/122	101/126	95/133	128/99	
Age (y)	42.2 ± 10.8[b]	44.7 ± 11.2	44.8 ± 10.6	47.7 ± 10.2	0.03	49.1 ± 9.6	44.8 ± 11.2	43.0 ± 10.7	42.4 ± 10.7	0.05
BMI (kg/m^2)	28.2 ± 5.5	28.4 ± 6,4	28.6 ± 5.9	28.7 ± 4,7	0.001	29.7 ± 5.8	27.9 ± 4.8	28.5 ± 5.9	27.8 ± 5.8	0.01
Weight at age 18-20 y	50.5 ± 17.5	50.8 ± 17.1	50.9 ± 17.4	52.9 ± 16.2	0.003	50.6 ± 17.1	52.4 ± 16.0	49.7 ± 18.1	52.3 ± 16.9	0.004
Age at menarche (y)	12.7 ± 3.6	12.8 ± 2.8	12.9 ± 2.8	13.5 ± 2.3	0.001	12.7 ± 2.8	13.0 ± 2.8	12.8 ± 2.8	13.0 ± 2.6	0.002
No. of children	2.2 ± 1.8	2.4 ± 1/8	2.4 ± 1.7	2.5 ± 1.6	0.002	2.7 ± 1.7	2.5 ± 1.8	2.1 ± 1.7	2.2 ± 1.7	0.01
Total energy (kcal)	3115.6 ± 1116.9	2427.8 ± 1048.1	2599.7 ± 905.3	2859.9 ± 1008.4	0.06	3050.6 ± 1128.9	2575.3 ± 973.6	2381 ± 924.4	2997.5 ± 1028.9	0.07
Carbohydrate (% of energy)	47.1 ± 12.4	51.8 ± 10.2	51.8 ± 9.1	52.4 ± 8.9	0.04	50.1 ± 12.0	50.2 ± 10.8	51.0 ± 9.31	51.7 ± 9.5	0.004
Protein (% of energy)	9.9 ± 2.9	12.4 ± 3.8	12.9 ± 3.1	13.8 ± 3.3	0.15	12.4 ± 4.1	12.2 ± 3.4	12.7 ± 3.7	11.9 ± 3.2	0.006
Fat (% of energy)	44.7 ± 13.8	37.9 ± 10.7	37.6 ± 9.4	36.1 ± 9.3	0.08	39.5 ± 13.4	39.7 ± 12.4	38.5 ± 9.9	38.7 ± 9.7	0.002
Fiber (g)	18.3 ± 8.2	19.6 ± 11.0	23.5 ± 7.8	31.9 ± 11.9	0.22	28.8 ± 14.4	21.5 ± 8.4	19.9 ± 9.5	23.2 ± 9.6	0.09
Physical activity level										
Low	141 (61.4)[c]	122 (53.7)	132 (57.8)	91 (40.09)	<0.0001	112 (49.1)	114 (50.2)	130 (57.0)	130 (57.2)	0.09
Moderate	59 (25.8)	75 (33.0)	59 (25.8)	81 (35.6)		77 (33.7)	75 (33.0)	69 (30.2)	53 (23.3).9	
Vigorous	28 (12.2)	30 (13.2)	37 (16.2)	55 (24.2)		39 (17.1)	38 (16.7)	29 (12.7)	44 (19.3)	
Education level										
None	31 (13.8)	31 (13.9)	20 (8.8)	16 (7.14)	0.1	29 (13.0)	27 (12.0)	21 (9.3)	21 (9.3)	0.35
Primary	56 (25.0)	59 (26.4)	59 (26.2)	51 (22.7)		61 (27.3)	49 (21.8)	58 (25.7)	57 (25.4)	
Secondary school	106 (47.3)	102 (45.7)	100 (44.4)	120 (53.5)		102 (45.7)	102 (45.5)	107 (47.5)	117 (52.2)	
University	31 (13.8)	31 (13.9)	46 (20.4)	37 (16.5)		31 (13.9)	46 (20.5)	39 (17.3)	29 (12.9)	
Marital status										
Unmarried	16 (7.0)	17 (7.4)	16 (7.0)	11 (4.8)	0.96	12 (5.2)	14 (6.17)	16 (7.0)	18 (7.9)	0.86
Married	189 (82.2)	183 (80.6)	188 (82.4)	190 (83.7)		186 (81.5)	187 (82.3)	187 (82.0)	190 (83.7)	
Divorced/widowed	17 (7.4)	22 (9.6)	20 (8.7)	22 (9.6)		24 (10.5)	22 (9.6)	19 (8.3)	16 (7.0)	
Family history of BC	12 (5.2)	13 (5.7)	6 (2.6)	17 (7.4)	0.13	16 (7.02)	7 (3.08)	11 (4.8)	14 (6.1)	0.25
Oral contraceptive use	116 (55.2)	117 (57.1)	113 (55.1)	125 (59.5)	0.66	108 (51.4)	118 (56.4)	124 (61.4)	121 (57.9)	0.31
Postmenopausal women	55 (25.3)	65 (29.9)	76 (35.1)	94 (43.1)	0.004	100 (45.8)	73 (33.4)	57 (26.5)	60 (27.6)	0.0001
Postmenopausal hormone use	1 (0.4)	5 (2.2)	3 (1.3)	2 (0.8)	0.35	2 (0.8)	3 (1.3)	5 (2.1)	1 (0.4)	0.36
Alcohol intake	10 (4.4)	8 (3.6)	11 (4.8)	12 (5.3)	0.84	8 (3.5)	12 (5.3)	9 (4.02)	12 (5.3)	0.73
Smoking status	11 (4.9)	7 (3.1)	9 (4.0)	13 (5.8)	0.67	10 (4.4)	7 (3.1)	7 (3.1)	16 (7.1)	0.07
Nulliparous/missing	96 (42.1)	107 (47.1)	9 8(42.9)	86 (37.8)	0.26	76 (33.3)	95 (41.8)	109 (47.8)	107 (47.1)	0.006

[a]: χ^2 Test for ordinal qualitative variables and ANOVA for continuous variables; [b]: Mean ± SD; [c]: N (%).

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Table 3. Dietary pattern and risk of BC

Dietary pattern	Quartile, all (n 946 breast cancer cases = 452)							
	Q1	Q2		Q3		Q4		*P*-trend[a]
	OR	OR	95%CI	OR	95%CI	OR	95%CI	
Healthy diet								
No. of cases (%)	124 (28.8)	113(26.3)		90(20.9)		103(23.9)		
Crude	1.00 (Ref)	0.83	0.57-1. 20	0.54	0.37-0.79	0.69	0.48-1.00	0.03
Age adjusted	1.00 (Ref)	0.76	0.52-1.11	0.51	0.34-0.74	0.61	0.41-0.88	0.006
Age and energy adjusted	1.00 (Ref)	0.79	0.53-1.16	0.52	0.35-0.76	0.61	0.41-0.89	0.006
Model 1[b]	1.00 (Ref)	0.86	0.57-1.31	0.58	0.38-0.88	0.61	0.41-0.92	0.008
Model 2[c]	1.00 (Ref)	0.84	0.55-1.27	0.56	0.37-0.84	0.57	0.37-0.86	0.003
Model 3[d]	1.00 (Ref)	0.93	0.59-1.48	0.59	0.37-0.92	0.52	0.33-0.82	0.001
Unhealthy diet								
No. of cases (%)	106 (24.6)	101(23.5)		95(22.1)		128(29.8)		
Crude	1.00 (Ref)	0.92	0.63-1.33	0.82	0.56-1.19	1.48	1.02-2.15	0.007
Age adjusted	1.00 (Ref)	0.99	0.68-1.45	0.94	0.64-1.38	1.73	1.17-2.54	0.001
Age and energy adjusted	1.00 (Ref)	1.02	0.69-1.49	0.97	0.65-1.44	1.74	1.18-2.56	0.001
Model 1[b]	1.00 (Ref)	1.01	0.66-1.52	1.02	0.66-1.56	1.82	1.20-2.76	0.001
Model 2[c]	1.00 (Ref)	1.05	0.69-1.59	1.05	0.68-1.63	1.87	1.23-2.86	0.001
Model 3[d]	1.00 (Ref)	1.26	0.80-1.99	1.33	0.83-2.15	1.96	1.23-3.10	0.004

[a]: P-trend is resulted from logistic regression test based on median values of each quartile; [b]: Adjusted for age, energy, family history of BC, BMI (continuously), menarche age, weight at age 18-20, menopausal status; [c]: further adjusted for marital status and parity; [d]: Additionally, adjusted for alcohol intake, menopausal hormone use, contraceptive use, cigarette smoking.

Table 4. Odds ratios for breast cancer risk across quartile categories of dietary pattern scores by menopausal status.

Dietary pattern	Quartile of dietary pattern score							
	Q1	Q2		Q3		Q4		
		OR	95%CI	OR	95%CI	OR	95%CI	*P*-trend[a]
Premenopause (n 576; cases = 285)								
Healthy dietary pattern								
Cases/controls	92/70	76/75		61/78		56/68		
Model 1[b]	1	0.79	0.48-1.29	0.59	0.36-0.96	0.52	0.31-0.87	0.008
Model 2[c]	1	0.82	0.50-1.34	0.59	0.36-0.97	0.51	0.30-0.85	0.006
Model 3[d]	1	0.89	0.52-1.53	0.59	0.34-1.02	0.47	0.26-0.83	0.004
Unhealthy dietary pattern								
Cases/controls	51/61	63/85		75/73		95/60		
Model 1[b]	1	1.12	0.65-1.94	1.59	0.91-2.78	2.55	1.48-4.40	<0.0001
Model 2[c]	1	1.13	0.65-1.97	1.62	0.92-2.84	2.56	1.48-4.42	<0.0001
Model 3[d]	1	1.51	0.83-2.76	2.27	1.22-4.23	2.85	1.57-5.17	<0.0001
Postmenopause (n 290; cases = 138)								
Healthy dietary pattern								
Cases/controls	28/27	36/29		28/48		46/48		
Model 1[b]	1	1.19	0.53-2.69	0.58	0.26-1.24	0.81	0.39-1.66	0.34
Model 2[c]	1	1.02	0.45-2.34	0.48	0.22-1.07	0.68	0.32-1.42	0.19
Model 3[d]	1	1.24	0.49-3.09	0.54	0.22-1.28	0.71	0.32-1.59	0.20
Unhealthy dietary pattern								
Cases/controls	50/50	37/36		20/37		31/29		
Model 1[b]	1	1.20	0.61-2.36	0.52	0.25-1.10	1.25	0.62-2.53	0.86
Model 2[c]	1	1.26	0.63-2.52	0.54	0.25-1.13	1.34	0.65-2.74	0.77
Model 3[d]	1	1.46	0.69-3.11	0.48	0.21-1.10	1.23	0.56-2.70	0.90

[a]: P-trend is resulted from logistic regression test based on median values of each quartile; [b]: Adjusted for age, energy, family history of BC, BMI (continuously), menarche age, weight at age 18-20, menopausal status; [c]: Further adjusted for marital status and parity; [d]: Additionally, adjusted for alcohol intake, menopausal hormone use, contraceptive use, cigarette smoking

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Discussion

The present study identified two major dietary patterns, named healthy and unhealthy dietary patterns. These extracted dietary patterns were similar to patterns found in a previous study in Iran that used the same FFQ (Hajizadeh *et al.*, 2010, Rezazadeh *et al.*, 2010). It was found that a healthy dietary pattern with high intake of fruits, fruit juices, cruciferous vegetables, yellow vegetables, tomato, green leafy vegetables, other vegetables, and garlic was associated with a decrease in the risk of BC. However, an unhealthy dietary pattern with high intake of processed meats, eggs, butter, refined grains, mayonnaise, hydrogenated fat, sugars, soft drinks, and pickles increased the risk of BC. These associations remained significant, even after stratifying by menopausal status, in premenopausal women.

The results found from previous studies regarding the association of BC risk and dietary pattern were inconsistent. Moreover, there are not several studies that can examine the association between BC risk and dietary patterns in Middle-Eastern countries. Most previous studies were conducted in developed countries and have derived different patterns (Adebamowo *et al.*, 2005, Agurs-Collins *et al.*, 2009, Baglietto *et al.*, 2011, Fung *et al.*, 2005, Harris *et al.*, 2017, Männistö *et al.*, 2005, Sieri *et al.*, 2004, Velie *et al.*, 2005). Only one case-control study with small sample size (100 cases-174 controls) assessed the association between dietary pattern and BC risk in Iran and found the relationship between a healthy and unhealthy dietary pattern with BC risk (Karimi *et al.*, 2014). In agreement with the present results, some case-control studies have illustrated an inverse association between the risk of BC and healthy or similar to healthy dietary pattern (De Stefani *et al.*, 2009, Hirose *et al.*, 2007, Murtaugh *et al.*, 2008, Ronco *et al.*, 2006, Wu *et al.*, 2009, Zhang *et al.*, 2011). A positive association have been distinguished between unhealthy or western dietary patterns and BC risk (Cui *et al.*, 2007, De Stefani *et al.*, 2009, Edefonti *et al.*, 2008, Murtaugh *et al.*, 2008, Ronco *et al.*, 2006, Wu *et al.*, 2009). The results of a recent meta-analysis on case-control studies indicated that a higher score of healthy pattern was associated with a decreased BC risk and higher adherence to unhealthy pattern was associated with a 33% increase in risk of BC (Grosso *et al.*, 2017). A number of studies explored the protective effects of fruits and vegetables against BC (Eliassen *et al.*, 2012, Fritz *et al.*, 2013, Gandini *et al.*, 2000, Gong *et al.*, 2014, Harris *et al.*, 2014, Wu *et al.*, 2013) that may have stemmed from high content of fiber and much amounts of antioxidants and certain photochemical which contribute to inhibition bio-activation of carcinogen, signaling of cell, cell cycle regulation, inflammation, and angiogenesis (Giacosa *et al.*, 2013). Fiber can improve insulin sensitivity (Tucker *et al.*, 2015) and decrease circulating insulin-like growth factors (Barnard *et al.*, 2006) that are related to BC risk. In addition, dietary fiber can inhibit colonic β-D-glucuronidase activity, which results in decreased deconjugation and reabsorption of oestrogen, thus decreasing plasma levels of oestrogen and increasing fecal excretion (Gerber, 1996, Rose *et al.*, 1991). In this context, the study patients had higher intake of refined grain and lower consumption of vegetables. Due to low price, carbohydrate intake, especially refined grain, is high among Iranian people compared to other food resources. However, a study on Chinese women reported a null association between vegetable-soy dietary pattern and risk of BC , which may resulted from different effects of raw and cooked vegetable on BC risk (Cui *et al.*, 2007). A prospective study identified that higher consumption of fruits and salad, as raw vegetables, was related with the reduced risk of BC (Baglietto *et al.*, 2011). Given that some micronutrients of fruits and vegetables are destroyed by cooking, raw and cooked vegetables were separated in the present analysis. A meta-analysis study demonstrated that red meat increased the risk of BC by 10% in the highest compared to lowest categories of intake, the corresponding number was 8% for processed meat (Guo *et al.*, 2015). While animal food pattern in premenopausal Japanese women (Kojima *et al.*, 2017) and pork, processed meat, potatoes pattern in the NLCS cohort (Van den Brandt *et al.*, 1990), had a protective effect against BC. Several possible mechanisms may identify the positive association between processed meat and BC risk. These mechanisms include the presence of pro-carcinogenic factors, such as salt, *N*-nitroso compounds, heme iron, heterocyclic amines (HCA), and polycyclic aromatic hydrocarbons (PAH), which are produced in high heat cooking of meat, in processed meat (Abid *et al.*, 2014, Kazerouni *et al.*, 2001, Knize *et al.*, 1999). Human studies have reported the positive association between intake of Polycyclic Aromatic Hydrocarbons (PAHs) and Heterocyclic Amines (HCAs) and BC risk (Bonner *et al.*, 2005, Zheng and Lee, 2009).

In addition, diet rich in refined grains, sugars, desserts and fatty dietary pattern particularly saturated fat may lead to increased blood glucose levels, body fats, and impaired hormonal homeostasis (Hirose *et al.*, 2007, Sieri *et al.*, 2014, Zhang *et al.*, 2011). Higher insulin regulation creates cellular proliferation and encourages tumor growth, also hyperinsulinemia indirectly leads to increased free oestrogen concentration resulting from inhibition of sex-hormone-binding globulin production (Bradshaw *et al.*, 2009).

In the present study, we could not observe a significant association between two major dietary patterns and BC risk among postmenopausal women. While, in premenopausal women healthy dietary patterns was inversely associated with BC risk and higher adherence to unhealthy dietary patterns was positively related to BC risk. In the current study premenopausal had higher refined grain than postmenopausal women ($P < 0.01$), which could result in hyperinsulinemia. Studies have illustrated that hyperinsulinemia can increase risk of BC via inhibiting apoptosis as well as by reducing production of sex hormone binding globulin, which can increase the level of free estrogen (Gupta *et al.*, 2002, Kaaks and Lukanova, 2001). A significant association was observed in premenopausal women, where hormonal factors predominate, which is consistent with the present study. However, Hankinson et al. in a review study stated that the relation between circulating levels of estrogen and testosterone and BC risk was well established in postmenopausal women (Hankinson and Eliassen, 2007). Most of the studies examined the relationship between BC risk and dietary patterns in postmenopausal women rather than premenopausal and observed null or statistical significant association (Cui *et al.*, 2007, Fung *et al.*, 2005, Velie *et al.*, 2005). The study in shanghai indicated that meat-sweet pattern (considering as unhealthy pattern) is positively associated with risk of BC in postmenopausal women (Cui *et al.*, 2007). In Japanese women a westernized dietary pattern as an unhealthy pattern was associated with 29% increased risk of BC among postmenopausal subjects (Shin *et al.*, 2016). A systematic review suggested that intake of Mediterranean dietary pattern (considering as a healthy pattern) was associated with reduced risk of postmenopausal BC (Coughlin *et al.*, 2018).

The present study has some limitations. First, selection bias is an inherent limitation in case-control studies. Although the case-control studies suffered from selection bias in the present study, the authors tried to reduce the bias. Moreover, the variables in the models as the matching factors almost well adjusted the effect of them on the outcome. Second, using factor analysis contained subjective or arbitrary decisions that should be considered. Third, dietary assessment has measurement errors due to limitations of FFQ. It was compensated using a validated FFQ and elimination of over and under reports of energy intake. Fourth, there were limited data on hormone receptor status of the patients and could not evaluate the risk of BC with considering the hormone receptor subtypes due to small power.

This study had several strengths. The participants were recruited from a general hospital where subjects refer from throughout the country. Control group consisted of those healthy women referring to the same hospital of case group and were match for age and residential place. Matching for residential place was necessary to avoid biases due to difference in the referral pattern between the case and control groups. A wide spectrum of confounding variables was adjusted. Assessment of overall diet in regards to a dietary pattern method, instead of the effects of individual nutrients or specific food group could be the study strength. The large sample size allowed the authors to study the associations in pre-and postmenopausal women exclusively.

Conclusion

The present study is the first large case-control study to examine the association between dietary patterns and risk of BC using factor analysis in the Middle-Eastern region. The results demonstrated a decreased risk of BC for healthy dietary pattern characterized by high intake of fruits, fruit juices, cruciferous vegetables, yellow vegetables, tomatoes, green leafy vegetables, other vegetables, and garlic and increased risk of BC for unhealthy dietary pattern among overall and premenopausal subjects. However, no significant association was observed between BC risk and dietary patterns in postmenopausal women. The results can be used to for population awareness and cancer prevention interventions.

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Authors' contribution

Sasanfar B and Toorang F participated in the study design, analysis and drafted the initial version. Nemati S and Mohebbi E helped in data analysis. Sasanfar B implemented comments and suggestions of the co-authors. Zendehdel K and Azadbakht L contributed to the conception, design and data analysis. All authors reviewed the final version of the manuscript. Zendehdel K and Azadbakht L supervised the study.

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Conflict of Interest

None of the authors declared any conflict of interest.

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Appendix 1. Food grouping used in the dietary pattern analyses

Food groups	Food items
Processed meats	Sausage, hamburger
Red meats	Beef, lamb
Organ meats	Beef liver, kidney, heart, brain
Fish	Canned tuna fish, other fish
Poultry	Chicken with or without skin
Eggs	Eggs
Butter	Butter
Margarine	Margarine
Low-fat dairy products	Skim or low fat milk, low fat yoghurt
High-fat dairy products	High-fat milk, whole milk, chocolate milk, cream, high-fat yoghurt, cream yoghurt, cream cheese, other cheese, ice cream, kashk
Tea	Tea
Coffee	Coffee
Fruits	Cantaloupe, melons, watermelon, pears, palms, cherries, apples, peaches, nectarine, grapes, kiwi, grapefruit, oranges, persimmons, tangerine, pomegranates, bananas, lemons, strawberries, fresh figs and dates
Fruit juices	Grapefruit juice, orange juice, apple juice, cantaloupe juice, lemon juice, pineapples, mulberry
Cruciferous vegetables	Cabbage, cauliflower, Brussels sprouts, kale
Yellow vegetables	Carrots, squash
Tomatoes	Tomatoes, tomato sauce
Green leafy vegetables	Lettuce, spinach, mixed vegetables
Other vegetables	Cucumber, eggplant, celery, green peas, green beans, green pepper, zucchini, bell pepper, turnip, corn, onion
Fried vegetables	Fried vegetables
Legumes	Beans, peas, lima beans, broad beans, lentils,
Soy	Soy
Garlic	Garlic, aged garlic
Potatoes	Potatoes
French fries	French fries
Whole grains	Dark breads (Sangak, Barbari, Taftoon), barley bread, oat bread, popcorn, bulgur, whole toasted bread
Refined grains	White breads (lavash, baguettes), noodles, pasta, rice, white flour, biscuits, milled barley
Pizza	Pizza
Snacks	Potato chips, crackers, popcorn
Nuts	Peanuts, almond, pistachios, hazelnuts, walnuts, roasted seeds
Mayonnaise	Mayonnaise
Dried fruit	Dried figs, dried dates, dried mulberries, dried apricots, dried peaches, raisins
Canned fruits	Canned pineapple, other canned fruits
Olives	Olives, olive oils
Sweets and desserts	Chocolates, cookies, cakes, confections, jam, sohan (a traditional Persian confectionery made of flour, egg, sugar, nuts and vegetable oil), creme caramel, halva
Hydrogenated fats	Hydrogenated fats
Vegetables oils	Vegetables oils (except for olive oil)
Animal fat	Animal fat
Sugars	Sugars, candies, jam, gaz (an Iranian confectionery made of sugar, nuts, and tamarisk)
Soft drinks	Soft drinks
Yogurt drink	Doogh
Spice	Black pepper
Pickles	Pickles

Appendix 2. Factor-loading matrix for major dietary patterns

Food groups	Dietary patterns		
	Healthy	**Unhealthy**	
Processed meats	-	0.406	
Red meats	-	-	
Organ meats	-	-	
Fish	-	-	
Poultry	-	-	
Eggs	-	0.323	
Butter	-	0.330	
Margarine	-	-	
Low-fat dairy products	-	-	
High-fat dairy products	-	-	
Tea	-	-	
Coffee	-	-	
Fruits	0.610	-	
Fruit juices	0.361	-	
Cruciferous vegetables	0.332	-	
Yellow vegetables	0.311	-	
Tomatoes	0.461	-	
Green leafy vegetables	0.520	-	
Other vegetables	0.586	-	
Fried vegetables	-	-	
Legumes	-	-	
Soy	-	-	
Garlic	0.372	-	
Potatoes	-	-	
French fries	-	-	
Whole grains	-	-	
Refined grains	-	0.384	
Pizza	-	-	
Snacks	-	-	
Nuts	-	-	
Mayonnaise	-	0.403	
Dried fruit	-	-	
Canned fruits	-	-	
Olives	-	-	
Sweets and desserts	-	-	
Hydrogenated fats	-	0.309	
Vegetables oils	-	-	
Animal fat	-	-	
Sugars	-	0.407	
Soft drinks	-	0.433	
Yogurt drink	-	-	
Spice	-	-	
Pickles	-	0.349	
Eigenvalue	2.7	1.3	
Variance explained by each factor	47.9	23.9	71.9

Loading <0.30 were omitted for simplicity