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Higher dietary acid load is not associated with risk of breast cancer in Iranian women

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Abstract

Background: Dietary acid load (DAL) may play a key role in certain cancers, including breast cancer (BC); however, evidence showing a causal relationship is lacking.

Aim: We examined the relationship between DAL, assessed with both the potential renal acid load (PRAL) and the net endogenous acid production (NEAP) scores, and BC risk.

Methods: We identified 150 women who had a diagnosis of BC recently and 150 age-matched apparently healthy controls. Data from dietary intake and anthropometric measures were collected from participants and eventually, PRAL and NEAP scores were obtained from nutrient intakes. Multivariate odds ratios (OR) with 95% confidence intervals (CI) were used to evaluate the relationship of BC risk with PRAL and NEAP scores.

Results: The odds ratios (OR) of BC according to tertiles of PRAL and NEAP scores by multivariate logistic regression models revealed that both PRAL (P-trend = 0.8) and NEAP (P-trend = 0.1) scores were not significantly associated with BC risk. After controlling confounders, multiple logistic regressions still remained non-significant which indicated no significant associations between PRAL (P-trend = 0.9), NEAP (P-trend = 0.4) scores and risk of BC.

Conclusion: The results of our study suggested that there is no significant relationship between DAL and BC incidence among Iranian women.

KEYWORDS

acid–base balance, breast cancer, dietary acid load, net endogenous acid production, potential renal acid load

1 | INTRODUCTION

Despite wide range of evidences, the role of diet in the risk breast cancer (BC) is still not entirely understood. Generally, higher consumption of red meat, alcohol and fat may be associated with BC incidence while diet rich in fiber, fruit, vegetable and different sources of phytoestrogens, broadly speaking a plant-based diet is known as a preventive dietary approach for BC.[1] The mechanisms proposed to explain the association between diet or dietary factors and risk of BC are broad.[1] In addition, it has been hypothesized that dietary acid load (DAL) of diet can influence the body's acid–base balance. The DAL concept hypothesizes that animal products, such as meat, dairy

Abbreviations: BC, breast cancer; CKD, chronic kidney disease; EGFR, epidermal growth factor receptors; ESRD, end stage renal disease; HRT, hormone replacement therapy; IGF-1, insulin-like growth factor-1; NEAP, net endogenous acid production; OCP, oral contraceptive; PRAL, potential renal acid load and eggs, create an acidic environment in the body while plant-based foods, such as fruits and vegetables provide a more alkaline environment. Overall DAL is estimated by net endogenous acid production (NEAP) and the potential renal acid load (PRAL).[2,3] While the literature has shown mixed results, there are studies showing an association between DAL and obesity, increased waist circumference, dyslipidemia,[4] and hypertension,[5] which are all risk factors for BC.[6-9] Moreover, there is limited evidence that an acidic environment may promote grows of some cancer cells and tumors.[10,11] But, until now, few studies have explored the association of diet-dependent acid load and the risk of cancer, especially BC. In this context, prior literature on 50,884 US and Puerto Rican women with the mean follow up 6.7 years, revealed that higher DAL which assessed by PRAL may be a risk factor for invasive BC, they proposed that base-inducing diets such as fruits and vegetables may have a protective effect on BC development while higher scores of PRAL which positively linked to meat and other acid-producing food consumption may be attributed as a risk factor for invasive BC.[12] In this study, dietary information was not updated during follow-up, so they could not evaluate any changes in dietary consumption over time. About the probable association between DAL and other kind of cancers, there is limited evidence. As only a cohort study assessed the link between renal net acid excretion and bladder cancer and indicated no significant association between renal net acid excretion and bladder cancer among on 27,096 male smokers after 17.4 years of follow-up.[13] Moreover, a systematic review provided no significant association between DAL and cancer incidence, they suggested that alkaline diet was not justified for preventing cancer.[14]

At present, according to findings of two studies on BC[12] and bladder cancer,[13] the associations of DAL and different cancer types have yielded inconsistent results. Also since, the nature of diet is different among populations and largely depends on the culture of geographical regions; we need to explore that type of association in different populations. In this context, a literature shows different dietary patterns across 187 nations in 1990 and 2010 and diet quality varies by age, sex, national income, time, and world region.[15] Although, a cohort study examined the association of diet-dependent acid load with BC among US and Puerto Rican women but up to date, no study have been examined the association between DAL and BC incidence in case–control design and among Iranian women. Hence, we conducted a population-based study to address the relation of DAL indicators including PRAL and NEAP with the risk of BC in Iranian women.

2 | METHODS

2.1 | Study population

The present case–control study was carried out on 150 women who had been recently diagnosed with BC and 150 apparently healthy women in cancer research center, Imam Khomeini hospital between September 23, 2017 and June 21, 2018. A pathologist referred cases to attend our study. On the other hand, through poster installation, apparently healthy subjects selected from relatives of patients in other wards of Imam Khomeini Hospital, such as dermatology, urology, orthopedic, etc., which had no family relationship with cases. The cases and controls were matched only by age. In order to decreasing the effect of awareness of BC on subject dietary reports, only women with diagnosis period of less than 3 months were included to our study. Also, cases and controls were excluded if they had medical history or presence of other cancers and controls that had BC history were not selected too. Two trained interviewers obtained information from participants by a 45-min structured face-to-face interview. They administered to cases and controls a structured questionnaire, including information on age (year), BMI (kg/m^2), education ($\leq$ high school or $\geq$ university degree), marital status (married or single/divorced/widowed), menopause status (yes or no), socioeconomic status (low or high/average), alcohol use (yes or no), smoking (yes or no), vitamin supplements and medication (lipid lowering and anti-hypertensive medications) uses (yes or no), medical history (diabetes, hypertension and hyperlipidemia) (yes or no), history of hormone replacement therapy (HRT) (yes or no) and time of oral contraceptive (OCP) use (year), age at first menarche (year), time since menopause in postmenopausal women (year), weight at age 18 years old (kg), number of child (n), length of breast feeding (year) and family history of BC (yes or no).

2.2 | Ethical statement

This research has been supported by Tehran University of Medical Sciences (TUMS) (Ethics No. IR.TUMS.VCR.REC.1396.2880). Also, all participants provided informed consent.

2.3 | Assessment of anthropometric, physical activity and blood pressure measurements

Body weight of women was measured with light clothes on, by using a digital weighing scale (Seca725 GmbH & Co. Hamburg, Germany) to the nearest 0.1 kg. Height was measured in a standing position to the nearest 0.5 cm while women wearing no shoes. The following formula was used to calculate the body mass index (BMI). Physical activity was determined by a short from International Physical Activity Questionnaire (IPAQ) to calculate the metabolic equivalent (MET) minute per week.[16] MET minute per week (MET/min/wk), the duration and frequency of physical activity days were multiplied by the MET value of the activity. Then, sum of the scores was calculated as the total exercise minute per week. Also, systolic and diastolic blood pressures (sBP and dBP) were measured twice by Breuer blood pressure equipment (BC 08, digital, Germany) after at least 10–15 minutes rest while sitting and the mean of them was calculated and used.

2.4 | Dietary intake assessment

The nutritional status of the participants was determined by a semi-quantative 147-item food frequency questionnaire (FFQ) which

TABLE 1 Characteristics of study participants between apparently healthy controls and cases with BC

Variables	Apparently healthy controls (n = 150)	Cases with BC (n = 150)	P-value[a]
BMI (kg/m^2)	28.2 ± 5.2	28.1 ± 4.6	0.8
Education, n (%)			0.2
High school ≥	129 (86)	122 (81)	
≤ university degree	21 (14)	28 (19)	
Socioeconomic status [†], n (%)			0.8
Low	134 (89)	135 (90)	
High/average	16 (11)	15 (10)	
Marital status, n (%)			0.2
Married	136 (90)	129 (86)	
Single, divorced or widowed	14 (10)	21 (14)	
Menopause status, yes, n (%)	61(40)	54 (36)	0.4
Time since menopause in post-menopausal women (year)	10.0 ± 8.3	8.7 ± 7.3	0.3
Age at first menarche (year)	13.6 ± 1.6	13.4 ± 1.6	0.3
Weight at 18 years old (kg)	51.4 ± 9.1	52.0 ± 8.9	0.5
Number of child, n	2.6 ± 2.1	2.4 ± 2.1	0.3
Length of breastfeeding (year)	4.2 ± 3.5	3.5 ± 2.7	0.059
Family history of breast cancer, yes, n (%)	30 (20)	39 (26)	0.2
History of HRT, n (%)	12 (8)	8 (5)	0.3
OCP use time (year)	1.3 ± 1.1	1.2 ± 1.0	0.2
Physical activity (MET/min/wk)	590.0 ± 843.8	475.8 ± 1043.2	0.2
Smoking, never smoked, n (%)	147 (98)	144 (96)	0.3
Alcohol, never used, n (%)	149 (99)	148 (98)	0.5
Dietary supplement use, yes, n (%)	80 (53)	84 (56)	0.6
Comorbidities [‡], n (%)	38 (25)	31 (20)	0.3
Medication use [§], yes, n (%)	64 (42)	62 (41)	0.8
Energy intake (kcal/d)	2914.1 ± 1159.0	2660.3 ± 799.6	0.02*
Sodium intake (g/day)	4891.1 ± 2258.4	4351.1 ± 1670.6	0.01*
Systolic blood pressure (mm/hg)	120.4 ± 10.8	120.2 ± 10.7	0.3
Diastolic blood pressure (mm/hg)	80.3 ± 10.3	80.2 ± 10.0	0.3

(Continues)

TABLE 1 (Continued)

BC, Breast Cancer

BMI, body mass index

HRT, hormone replacement therapy

OCP, oral contraceptive

kg/m^2, kilogram/meter^2

MET/min/wk, metabolic equivalent minute per week

kcal/d, kilocalorie/day

g/day, gram/day

mg, milligram

mm/Hg, millimetre of mercury

[a]Student t test used for continuous variables, Chi-square test used for categorical variables.

[†]Diabetes, Hypertension and Hyperlipidemia

[‡]Socioeconomic status represents: having 3 or less living items for low status, 4 to 6 living items for average status, and 7 to 9 living items at home for high status

[§]Lipid lowering and anti-hypertensive medications

*P < 0.05.

**P < 0.01.

***P < 0.001.

previously validated in Iran for energy and nutrient intake.[17] Trained interviewers asked each woman to report how often, on average, they have consumed each food item on a daily, weekly, monthly or yearly scale over the previous year. Portion sizes of consumed foods that were reported in household measures were then converted to grams.

2.5 | Measuring dietary acid load

PRAL and NEAP are two major factors describing DAL. PRAL is an estimation of the production of endogenous acid that exceeds the level of alkali produced and depends on foods consumed daily.[18] Substantially, meats, eggs and dairy products are known as acid- while most fruits and vegetables are base- producing foods.[19] PRAL of food intakes was calculated by data obtained from the 147-item FFQ, using the calculation model developed by Remer and Manz:

[PRAL (mEq/d) = 0.49*protein(g) + 0.037*phosphorus (mg)]-0.021*potassium (mg) 0.026*magnesium (mg)-0.0125*calcium (mg)].[20]

The nonvolatile acid load, also known as the NEAP, is calculated by the balance of acid and alkali precursors in the diet.[21] In present

TABLE 2 Characteristic of study participants according to tertiles of potential renal acid load (PRAL)

	Tertile 1 (*n* = 100)	Tertile 2 (n = 100)	Tertile 3 (n = 100)	P-value [a]
PRAL (mEq/d)	−54.5 ± 4.4	−26.1 ± 2.3	−2.37 ± 4.07	
Age (year)	45.9 ± 9.3	46.5 ± 11.5	47.4 ± 11.2	0.6
BMI (kg/m^2)	29.1 ± 5.0	27.9 ± 4.8	27.5 ± 4.8	0.058
Education, n (%)				0.6
High school≥	84 (84)	81 (81)	86 (86)	
≤ university degree	16 (16)	19 (19)	14 (14)	
SociSocioeconomic status ‡, n (%)				0.6
Low	89 (89)	88 (88)	92 (92)	
High/average	11 (11)	12 (12)	8 (8)	
Marital status, n (%)				0.5
Married	85 (87)	93 (91)	87 (85)	
Single/divorced/widowed	12 (13)	9 (9)	14 (15)	
Menopause status, yes, n (%)	36 (37)	40 (39)	39 (48)	0.8
Time since menopause in post-menopausal women (year)	6.8 ± 6.0	9.7 ± 7.5	11.3 ± 9.0	0.04*
Age at first menarche (year)	13.5 ± 1.4	13.4 ± 1.5	13.6 ± 1.9	0.7
Weight at 18 years old (kg)	52.8 ± 9.0	52.0 ± 9.6	50.3 ± 8.2	0.1
Number of child, n	2.5 ± 1.7	2.5 ± 2.0	2.5 ± 2.1	0.9
Length of breastfeeding (year)	4.1 ± 3.1	3.7 ± 3.1	3.7 ± 3.1	0.5
Family history of breast cancer, yes, n (%)	16%	26%	27%	0.1
History of HRT, n (%)	6%	7%	7%	0.9
OCP use time (year)	1.1 ± 1.0	1.2 ± 0.9	1.3 ± 1.2	0.3
Physical activity (MET/min/wk)	598.5 ± 973.4	446.6 ± 666.2	553.7 ± 1147.0	0.5
Smoking, never smoked, n (%)	99%	97%	95%	0.2
Alcohol, never used, n (%)	100%	98%	99%	0.3
Dietary supplement use, yes, n (%)	51%	57%	56%	0.6
Comorbidities ‡, n (%)	20 (20.0)	21 (21.0)	28 (28.0)	0.3
Medication use §, yes, n (%)	43%	37%	46%	0.4
Energy intake (kcal/d)	2933.1 ± 1192.6	2603.5 ± 647.9	2825.0 ± 1064.7	0.06
Sodium intake (g/d)	4660.3 ± 2171.9	4205.4 ± 1180.4	4997.6 ± 2380.7	0.01*
Systolic blood pressure (mm/hg)	120.1 ± 10.5	120.4 ± 10.9	120.4 ± 10.7	0.5
Diastolic blood pressure (mm/hg)	80.3 ± 10.2	80.4 ± 10.0	80.2 ± 10.3	0.4

PRAL, potential renal acid load

mEq/d, milliequivalent/day

BMI, body mass index

HRT, hormone replacement therapy

OCP, oral contraceptive

kg/m^2, kilogram/meter^2

MET/min/wk, metabolic equivalent minute per week

kcal/d, kilocalorie/day

g/d, gram/day

mg, milligram

mm/Hg, millimetre of mercury

[a]ANOVA test used for continuous variables, Chi-square test used for categorical variables.

[†]Diabetes, Hypertension and Hyperlipidemia

[‡]Socioeconomic status represents: having 3 or less living items for low status, 4 to 6 living items for average status, and 7 to 9 living items at home for high status

§Lipid lowering and anti-hypertensive medications

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

study NEAP was estimated using a previously validated equation: [NEAP (mEq/d) = −10.2 + 54.5 (protein intake [g/d] ÷ potassium intake [mEq/d])].[22]

As mentioned above, different variables are used to calculate DAL in these formulas, and there is still no consistency for more credibility of one of them, so we used both of them in the present study.

2.6 | Statistical analyses

The SPSS version 23.0 for Windows was used in order to perform the statistical analysis. All individuals were categorized according to the tertiles of PRAL and NEAP. Characteristic and dietary intakes of participants were tested between case and control by Student t tests. Chi-square tests also were performed for comparing qualitative variables. The mean values of the quantitative variables across the tertiles were compared using the ANOVA test. Moreover, the mean intakes of main food groups which can affect acid–base status were compared between cases and controls. Logistic regressions were used to analyze the association between PRAL and NEAP and risk of BC after energy adjustment by the residual method. The results were adjusted for BMI (kg/m2), education (≤ high school or ≥ university degree), marital status (married or single/divorced/widowed), menopause status (yes or no), socioeconomic status (low or high/average), alcohol use (yes or no), smoking (yes or no), vitamin supplements and medication (lipid lowering and anti-hypertensive medications) uses (yes or no), medical history (diabetes, hypertension and hyperlipidemia) (yes or no), history of HRT (yes or no) and time of OCP use (year), age at first menarche (year), time since menopause in post-menopausal women (year), weight at age 18 years old (kg), number of child (n), length of breast feeding (year) and family history of BC (yes or no). The level of significance was set at 0.05.

3 | RESULTS

A total of 300 participants, 150 cases with BC and 150 apparently healthy control subjects were included in this analysis. The characteristics of study participants are shown in Table 1. It was shown that the mean dietary intake of energy (P = 0.02) and sodium (P = 0.01) were higher in healthy women compared to cases with BC. In addition, the baseline participant characteristics across the tertiles of PRAL and NEAP are shown in Table 2 and Table 3. It was observed that by increasing the score of PRAL, the time since menopause in post-menopausal women was increasing too (P = 0.04). Through tertiles of NEAP, the dietary intake of energy was significantly increased (P = 0.03). Interestingly, in both tertiles of NEAP (P < 0.001) and PRAL (P = 0.01) women in the highest tertiles had greater intake of sodium. Moreover, the result of Pearson correlation coefficient indicated that the correlation between PRAL and NEAP was significant (Pearson correlation coefficient = 0.81, P < 0.001). It was also observed that individuals with BC noticeably consumed more red and processed meat in comparison to healthy ones (P = 0.01) while the consumption of other food groups did not differ significantly between two groups Table 4.

The odds ratios (OR) of BC according to tertiles of PRAL and NEAP by multivariate logistic regression models are presented in Table 5. Our crude results manifested that both PRAL (P-trend = 0.8) and NEAP (P-trend = 0.1) were not significantly linked to BC risk. After controlling known risk factors for BC such as BMI, education, marital status, menopause status, socioeconomic status, alcohol use, smoking, vitamin supplements and medication (lipid lowering and anti-hypertensive medications) uses, medical history (diabetes, hypertension and hyperlipidemia), history of HRT and time of OCP use, age at first menarche, time since menopause in post-menopausal women, weight at age 18 years old, number of child, length of breast feeding, family history of BC and energy intake, multiple logistic regressions indicated no statistical significant associations between PRAL (P-trend = 0.9), NEAP (P-trend = 0.4) and risk of BC too.

4 | DISCUSSION

To our knowledge, this is the first study which examined the relationship between the acid–base potential of diet and risk of BC in a case–control study of Iranian women. We found that diet-dependent acid load was not significantly associated with the increased risk BC in Iranian women.

Nevertheless, few studies evaluated the association of acidosis and cancer risk.[12-14,23] For example, Park et al.[12] used PRAL and NEAP to estimate DAL, recognized that women in highest quartile of PRAL and NEAP were more susceptible for invasive BC incidence. Although, this study did not provide data of possible association of NEAP and BC risk. The mentioned relationship was more pronounced in post-menopausal status and in estrogen and progesterone receptor negative BC[12] but in the present study there was a limitation of access to information of tumor receptor status. Regarding to another type of cancer, in line with our study, Wright et al.[13] examined the relation between urine pH and the risk of bladder cancer found a significant association of net acid excretion on bladder cancer incidence. Therefore, at present, very little evidence has been supported the hypothesis of the existence a relationship between DAL and cancer risk. Moreover, in line with our result, recent systematic review revealed no significant relationship between alkaline diet and water and cancer risk[14] while another review indicated there was a relationship acid–base

TABLE 3 Characteristic of study participants according to tertiles of net endogenous acid production (NEAP)

	Tertile 1(n = 100)	Tertile 2(n = 100)	Tertile 3 (n = 100)	P-value [a]
NEAP (mEq/d)	21.9 ± 3.5	29.4 ± 1.8	40.5 ± 7.5	
Age (year)	45.2 ± 9.2	47.5 ± 11.7	47.0 ± 11.0	0.2
BMI (kg/m^2)	28.7 ± 4.6	27.9 ± 5.6	27.8 ± 4.5	0.3
Education, n (%)				0.1
≥high school	87 (84)	78 (81)	86 (86)	
≥ university degree	13 (16)	22 (19)	14 (14)	
SociSocioeconomic status [‡], n (%)				0.8
Low	91 (91)	89 (89)	89 (89)	
High/average	9 (9)	11 (11)	11 (11)	
Marital status, n (%)				0.7
Married	87 (87)	88 (88)	90 (90)	
Single, divorced or widowed	13 (13)	12 (12)	10 (10)	
Menopause status, yes, n (%)	32 (37)	43 (39)	40 (48)	0.2
Time since menopause in post-menopausal women (year)	6.9 ± 6.1	9.9 ± 7.0	10.8 ± 9.5	0.09
Age at first menarche (year)	13.6 ± 1.4	13.4 ± 1.4	13.6 ± 1.9	0.5
Weight at 18 years old (kg)	52.5 ± 9.6	51.1 ± 8.4	51.5 ± 9.0	0.5
Number of child, n	2.5 ± 1.7	2.4 ± 1.8	2.6 ± 2.6	0.8
Length of breastfeeding (year)	4.1 ± 3.1	3.7 ± 3.1	3.7 ± 3.1	0.7
Family history of breast cancer, yes, n (%)	19%	25%	25%	0.5
History of HRT, n (%)	7%	6%	7%	0.9
OCP use time (year)	1.1 ± 1.0	1.2 ± 0.9	1.3 ± 1.2	0.3
Physical activity (MET/min/wk)	605.9 ± 1018.5	406.1 ± 587.6	586.8 ± 1145.5	0.2
Smoking, never smoked, n (%)	99%	97%	95%	0.2
Alcohol, never used, n (%)	100%	98%	99%	0.3
Dietary supplement use, yes, n (%)	51%	62%	51%	0.6
Comorbidities [‡], n (%)	19 (20.0)	25 (21.0)	25 (28.0)	0.5
Medication use [§], yes, n (%)	38%	44%	44%	0.6
Energy intake (kcal/d)	2625.3 ± 1142.8	2750.1 ± 752.9	2986.2 ± 1045.0	0.03*
Sodium intake (g/d)	4156.1 ± 2061.4	4449.2 ± 1418.5	5258.0 ± 2275.5	<0.001***
Systolic blood pressure (mm/hg)	120.1 ± 10.6	120.4 ± 10.8	120.5 ± 10.8	0.1
Diastolic blood pressure (mm/hg)	80.3 ± 10.1	80.3 ± 10.1	80.2 ± 10.3	0.8

NEAP, net endogenous acid production

mEq/d, milliequivalent/day

BMI, body mass index

HRT, hormone replacement therapy

OCP, oral contraceptive

kg/m2, kilogram/meter2

MET/min/wk, metabolic equivalent minute per week

kcal/d, kilocalorie/day

g/d, gram/day

mg, milligram

mm/Hg, millimetre of mercury

[a]ANOVA test used for continuous variables, Chi-square test used for categorical variables.

[†]Diabetes, Hypertension and Hyperlipidemia

[‡]Socioeconomic status represents: having 3 or less living items for low status, 4 to 6 living items for average status, and 7 to 9 living items at home for high status

[§]Lipid lowering and anti-hypertensive medications

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

TABLE 4 Mean intakes of main food groups contributing to acid–base balance between apparently healthy controls and cases with BC

Variables	Apparently healthy controls (n = 150)	Cases with BC(n = 150)	P-value †
Fruits[a] (g/d)	700.0 ± 287.5	701.3 ± 269.7	0.9
Vegetables[b] (g/d)	397.1 ± 171.3	373.7 ± 138.5	0.1
Red and processed meat[c] (g/d)	16.2 ± 12.0	20.5 ± 18.2	0.01*
Grains[d] (g/d)	562.7 ± 301.3	536.6 ± 248.2	0.4
Eggs (g/d)	19.8 ± 15.9	18.4 ± 16.4	0.4
Dairy products[e] (g/d)	378.5 ± 198.2	357.9 ± 223.5	0.3

[a]Watermelon, melon, apple, apricot, fig, nectarine, peach, pear, citrus fruit, date, kiwi, pomegranate, persimmon, prunes, grape, strawberry, banana, berries, grapefruit, cherries, orange juice, apple juice, lemon juice and other fruits.

[b]Spinach, lettuce, mixed vegetable, stew vegetables, local vegetables, kinds of cabbage, celery, carrots, pumpkin, eggplant, green squash, pepper, cucumber, garlic, tomato, onion, mushroom, green peas, green beans,turnip, and other vegetables.

[c]Beef, hamburger, lamb and sausages.

[d]White bread (all types), noodles, pasta, rice, milled barley, sweet bread, white flour, starch, cornflakes, corn, wheat germ, bulgur and potato.

[e]Skim or low-fat milk, low-fat yogurt, high-fat milk, whole milk, chocolate milk, cream, high-fat. yogurt, cream yogurt, cream cheese, other cheeses and ice cream.

BC, Breast Cancer

g/d, gram/day

†Student t test

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

balance and cancer occurrence or progression.[23] Additionally, we found that there was a direct association between PRAL and time since menopause which can propose that by increasing the time from menopause, the consumption of plant-based food was decreased. Consistent with our results which demonstrated higher PRAL score and probably lower consumptions of fruits and vegetables by increasing time since menopause, the finding of NHANES III study on 4,622 participants indicated that social isolation, missing teeth pairs and obesity may cause a reduction of fruits and vegetables consumptions among older adults.[24] Furthermore, we observed a positive link of NEAP score with daily energy intake. It confirmed that through increasing of DAL, the consumptions of energy-dense foods such as refined grains, added sugars, or fats are increased in individuals while the consumption of more fruits and vegetables typically lowers the DAL.[25,26] Although, this increasing trend of energy intake was not reflected in BMI which can be justified by short term data collection or bias of food recall in present study. Likewise, we observed that the intake of sodium was increased by higher PRAL and NEAP scores. In this context, a study defined that NaCl content of the diet contributed to low-grade metabolic acidosis in healthy subjects and NaCl had about 50–100% of the acidosis-producing effect of the diet net acid load.[27] However, we found that healthy subjects consumed more dietary sodium relative to cases. Also we observed that the consumption of red and processed meat was noticeably higher in cases with BC and about the probable relationship between meat consumption and BC incidence, the result of a meta-analysis including 12 prospective studies indicated that intake of red and processed meat was directly linked to BC risk.[28]

There are several possible explanations why we might did not find any association between DAL and BC risk. Evidences have proposed that the association of risk factors may be depended on the tumor receptor status[29,30] and previous studies found a more potent relationship between DAL and ER- and triple-negative BC.[12] We did not evaluate BC risk with considering hormone receptor status and it should be mentioned that this will require the inclusion of more patients and controls. Previous studies have proposed the potential effect of diet in adolescent on woman's future BC risk.[31,32] Given the limitations of food recall surveys, our study only examined dietary intake over a limited period of time. Therefore, the influence of diet over the lifespan, including childhood and adolescent periods, could not be accounted for. On the other hand, the intakes of fruits and

TABLE 5 Odds ratio (95% CI) of breast cancer according to tertiles of potential renal acid load (PRAL) and net endogenous acid production (NEAP)

Scores	Tertile 1 (*n* = 100)	Tertile 2 (n = 100)		Tertile 3 (n = 100)		P-trend*
PRAL (mEq/d)	−54.5 ± 24.5	−26.1 ± 3.8		−2.3 ± 16.3		
Subject with breast cancer (n)	48	56		46		
Model 1	1 ref	1.37	(0.79–2.40)	0.92	(0.53–1.60)	0.8
p		0.2		0.7		
Model 2	1 ref	1.64	(0.51–5.30)	1.00	(0.29–3.36)	0.9
P		0.4		0.9		
NEAP (mEq/d)	21.9 ± 3.5		29.4 ± 1.8		40.5 ± 7.5	
Subject with breast cancer (n)	52		56		42	
Model 1	1 ref	1.17	(0.67–2.05)	0.66	(0.38–1.16)	0.1
p		0.5		0.1		
Model 2	1 ref	3.94	(1.11–13.98)	0.92	(0.25–3.36)	
		0.03		0.9		0.4

CI, confidence interval

PRAL, potential renal acid load

NEAP, net endogenous acid production

mEq/d, milliequivalent/day

Model 1: unadjusted

Model 2: adjusted for BMI (kg/m2), education (≤ high school or ≥ university degree), marital status (married or single/divorced/widowed), menopause status (yes or no), socioeconomic status (low or high/average), alcohol use (yes or no), smoking (yes or no), vitamin supplements and medication (lipid lowering and anti-hypertensive medications) uses (yes or no), medical history (diabetes, hypertension and hyperlipidemia) (yes or no), history of HRT (yes or no) and time of OCP use (year), age at first menarche (year), time since menopause in post-menopausal women (year), weight at age 18 years old (kg), number of child (n), length of breast feeding (year), family history of BC (yes or no) and energy intake (kcal/day)

*P-trend <0.05.

vegetables which affect DAL is also related to socioeconomic status.[33] It was shown that fruits and vegetables intakes are positively associated with education and socioeconomic status[34] while we did not find any significant association between socioeconomic status and fruits and vegetables consumptions.

To the best of our knowledge, this is the first case–control study to evaluate the association between PRAL, NEAP and BC risk. Since age is one of the most prominent factor on BC incidence,[35] the strength of our study is a large number of subjects which adjusted by age. However, our study has further limitations. First, response errors, recall, social desirability and Berkson's bias are inevitable in the FFQ. Second, possible sampling bias and short period of assessment without any follow up time are other limitations. Third, we matched case and controls only by age. Although we tried to control those confounders, always there are some residual confounders. Also, similar to all case–control studies, no cause and effect association could be interpreted between DAL and BC.

5 | CONCLUSION

Our findings showed no significant association between DAL, assessed by PRAL and NEAP, with BC risk among Iranian women. Further examination of this association is warranted in other studies, exclusively with consideration of hormone receptor status.

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CONFLICT OF INTEREST

None declared.

AUTHORS' CONTRIBUTION

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, S.S.B.; *Methodology*, M.S., R.O., H.I.; *Investigation*, M.S., M.Y.; *Formal Analysis*, H.I.; *Resources*, R.O., M.S.; *Writing - Original Draft*, S.S.B., M.S.; *Writing - Review & Editing*, M.S., R.O., H.I., M.Y., S.S.B.; *Visualization*, M.S.; *Supervision*, S.S.B.; Funding Acquisition, not applicable.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Kotepui M. Diet and risk of breast cancer. *Contemp Oncol*. 2016;20(1):13-19.
2. Clinical disorders of fluid and electrolyte metabolism. *Calif Med*. 1963;99(2):155-156.
3. Remer T, Dimitriou T, Manz F. Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. *Am J Clin Nutr*. 2003;77(5):1255-1260.
4. Bahadoran Z, Mirmiran P, Khosravi H, Azizi F. Associations between dietary Acid-Base load and Cardiometabolic risk factors in adults: the Tehran lipid and glucose study. *Endocrinol Metab (Seoul, Korea)*. 2015;30(2):201-207.
5. Zhang L, Curhan GC, Forman JP. Diet-dependent net acid load and risk of incident hypertension in United States women. *Hypertension*. 2009;54(4):751-755.
6. Han H, Guo W, Shi W, et al. Hypertension and breast cancer risk: a systematic review and meta-analysis. *Sci Rep*. 2017;7(1):44877-44877.
7. Gravena AAF, Romeiro Lopes TC, de Oliveira Demitto M, et al. The obesity and the risk of breast Cancer among pre and postmenopausal women. *Asian Pac J Cancer Prev*. 2018;19(9):2429-2436.
8. Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' health study. *Am J Epidemiol*. 1999;150(12):1316-1324.
9. Schairer C, Freedman DM, Gadalla SM, Pfeiffer RM. Lipid-lowering drugs, dyslipidemia, and breast cancer risk in a Medicare population. *Breast Cancer Res Treat*. 2018;169(3):607-614.
10. McCarty MF, Whitaker J. Manipulating tumor acidification as a cancer treatment strategy. *Altern Med Rev*. 2010;15(3):264-272.
11. Gillies RJ, Raghunand N, Garcia-Martin ML, Gatenby RA. pH imaging. A Review of pH Measurement Methods and Applications in Cancers. *IEEE Eng Med Biol Mag*. 2004;23(5):57-64.
12. Park YM, Steck SE, Fung TT, et al. Higher diet-dependent acid load is associated with risk of breast cancer: findings from the sister study. *Int J Cancer*. 2019;144(8):1834-1843.
13. Wright ME, Michaud DS, Pietinen P, Taylor PR, Virtamo J, Albanes D. Estimated urine pH and bladder cancer risk in a cohort of male smokers (Finland). *Cancer Causes Control*. 2005;16(9):1117-1123.
14. Fenton TR, Huang T. Systematic review of the association between dietary acid load, alkaline water and cancer. *BMJ Open*. 2016;6(6):e010438.
15. Imamura F, Micha R, Khatibzadeh S, et al. Dietary quality among men and women in 187 countries in 1990 and 2010: a systematic assessment. *Lancet Glob Health*. 2015;3(3):e132-e142.
16. Committee IPAQR. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ); 2008.
17. Esmaillzadeh A, Mirmiran P, Azizi F. Whole-grain intake and the prevalence of hypertriglyceridemic waist phenotype in Tehranian adults. *Am J Clin Nutr*. 2005;81(1):55-63.
18. Remer T, Manz F. Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein. *Am J Clin Nutr*. 1994;59(6):1356-1361.
19. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005;81(2):341-354.
20. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc*. 1995;95(7):791-797.
21. Frassetto LA, Lanham-New SA, Macdonald HM, et al. Standardizing terminology for estimating the diet-dependent net acid load to the metabolic system. *J Nutr*. 2007;137(6):1491-1492.
22. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *Am J Clin Nutr*. 1998;68(3):576-583.
23. Robey IF. Examining the relationship between diet-induced acidosis and cancer. *Nutr Metab*. 2012;9(1):72-72.
24. Sahyoun NR, Zhang XL, Serdula MK. Barriers to the consumption of fruits and vegetables among older adults. *J Nutr Elder*. 2005;24(4):5-21.
25. Goraya N, Simoni J, Jo C, Wesson DE. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. *Kidney Int*. 2012;81(1):86-93.
26. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients--absence of evidence or evidence of absence? *Clin J Am Soc Nephrol*. 2008;3(1):226-236.
27. Frassetto LA, Morris RC Jr, Sebastian A. Dietary sodium chloride intake independently predicts the degree of hyperchloremic metabolic acidosis in healthy humans consuming a net acid-producing diet. *Am J Physiol Renal Physiol*. 2007;293(2):F521-F525.
28. Guo J, Wei W, Zhan L. Red and processed meat intake and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat*. 2015;151(1):191-198.
29. Baglietto L, Krishnan K, Severi G, et al. Dietary patterns and risk of breast cancer. *Br J Cancer*. 2011;104(3):524-531.
30. Agurs-Collins T, Rosenberg L, Makambi K, Palmer JR, Adams-Campbell L. Dietary patterns and breast cancer risk in women participating in the black Women's health study. *Am J Clin Nutr*. 2009;90(3):621-628.
31. Liu Y, Colditz GA, Cotterchio M, Boucher BA, Kreiger N. Adolescent dietary fiber, vegetable fat, vegetable protein, and nut intakes and breast cancer risk. *Breast Cancer Res Treat*. 2014;145(2):461-470.
32. Linos E, Willett WC, Cho E, Frazier L. Adolescent diet in relation to breast cancer risk among premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2010;19(3):689-696.
33. Abdollahi M, Mohammadi-Nasrabadi F, Houshiarrad A, Ghaffarpur M, Ghodsi D, Kalantari N. Socio-economic differences in dietary intakes: the comprehensive study on household food consumption patterns and nutritional status of IR Iran. *Nutr Food Sci Res*. 2014;1(1):19-26.
34. Irala-Estevez JD, Groth M, Johansson L, Oltersdorf U, Prattala R, Martinez-Gonzalez MA. A systematic review of socio-economic differences in food habits in Europe: consumption of fruit and vegetables. *Eur J Clin Nutr*. 2000;54(9):706-714.
35. Ozsoy A, Barca N, Dolek BA, et al. The relationship between breast Cancer and risk factors: a single-center study. *Eur J Breast Health*. 2017;13(3):145-149.

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