Dietary acid load and risk of prostate cancer: (a case-control study)

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Abstract

Background: There are few studies which have shown inconsistent results regarding the associations between dietary acid load (DAL) and the risk of cancer. This study aimed to examine the association between DAL and prostate cancer (PC) risk among Iranian population. Methods: One hundred and twenty participants (60 controls and 60 newly diagnosed PC patients) engaged in a hospital-based case-control study. Validated 160-items semi-quantitative food frequency questionnaire (FFQ) was used to assess usual dietary intakes. DAL was calculated using potential renal acid load (PRAL) and the net endogenous acid production (NEAP). Multivariate logistic regression was used to estimate the odds ratios. Results: Both PRAL (OR=5.44; 95% CI= (2.09-14.17)) and NEAP (OR=4.88; 95% CI= (2.22-13.41)) were associated with increased risk of PC in crude model. After adjusting for potential confounders (energy intake, smoking, physical activity, ethnicity, job, education, and some drugs usage) compared to the first category, being in the third category of PRAL (OR=3.42; 95% CI= (1.11-8.65)) and NEAP (OR=3.88; 95% CI= (1.26-9.55)) was associated with increased risk of PC. Conclusions: Our findings suggest that DAL could be associated with increased risk of PC. However, further prospective studies with larger sample sizes and longer durations are needed to confirm these findings.

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Results: Both PRAL (OR=5.44; 95% CI= (2.09-14.17)) and NEAP (OR=4.88; 95% CI= (2.22-13.41)) were associated with increased risk of PC in crude model. After adjusting for potential confounders (energy intake, smoking, physical activity, ethnicity, job, education, and some drugs usage) compared to the first category, being in the third category of PRAL (OR=3.42; 95% CI= (1.11-8.65)) and NEAP (OR=3.88; 95% CI= (1.26-9.55)) was associated with increased risk of PC.

Conclusions: Our findings suggest that DAL could be associated with increased risk of PC. However, further prospective studies with larger sample sizes and longer durations are needed to confirm these findings.

What is already known about this topic? The association between dietary acid load and several cardiovascular risk factors has been investigated previously but few studies investigated the association between diet-dependent acid load with cancer.**What does this article add?** Our findings showed that DAL could be associated with increased risk of PC

Keywords: Dietary acid load, NEAP, PRAL, Prostate cancer, Case-control.

Introduction

Prostate cancer (PC) is one of the major health concerns among men globally (1). It is presently the second most frequent diagnosed cancer and the sixth leading cause of cancer death for males worldwide (2-5). Among the Iranian males, PC is recognized as the third most prevalent malignancies and the six common cancer in Iranian population (6, 7). Based on the latest systematic review and meta-analysis on the available evidence, the incidence rate of prostate cancer is 7.1 per 100 000 in Iranian population. However, it has also been showed that the rate of disease incidence increased from 1996 to 2012 that should be noticed regarding the epidemiological and clinical practices (8). Well-known risk factors for prostate cancer are age, ethnicity, and family history of the disease (9). However, some other risk factors such as diet, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation, and occupational exposure might be involved in the pathogenesis of the disease(10).

The association between dietary patterns and the risk of PC has been investigated in several studies, which has led to inconsistent results. Some studies showed that adherence to a Western dietary pattern could increase the risk of prostate cancer (11-15), but others did not find any associations (16-18). In addition, some studies showed inconsistent findings about the association between healthy eating index and Mediterranean dietary pattern and the risk of PC (11, 13, 14, 16-23). Recently, the importance of dietary acid load is highlighted as the evidence shows that dietary intake is a key factor in the regulation of body's acid-base status (24, 25) and the kidneys are the main route of excretion of the acid load to maintain acid-base balance (26). Basically, it seems that western diets (with higher meat consumption), and healthy diets (with higher fruits and vegetables consumption and lower meat and processed grain intake) are associated with the acidic and alkali status of the diets, respectively (25, 27). In order to estimate dietary acid load, the potential renal acid load (PRAL) and the net endogenous acid production (NEAP), calculate from dietary intake (24, 28). The association between dietary acid load and several cardiovascular risk factors has been investigated previously (29-33). However, few studies investigated the association between diet-dependent acid load with

cancer (34, 35). Therefore, we aimed to investigate the association between diet-dependent acid load and risk of PC in Iranian population.

Materials and Methods

Subjects

This hospital based case-control study carried out in Shiraz, Iran. For this, 125 men (62 cases and 63 controls), who were referred to two main hospitals (teaching and referral hospitals) in Shiraz, Iran were recruited. To collect required information such as general characteristics and dietary intakes, the patients were interviewed by trained interviewers during their hospital stay Patients with PC who were candidate for radical or open prostatectomy were selected as cases based on the following inclusion criteria: persons without any history of dietary regimens for chronic diseases, diabetes, or other types of cancers and who their diseases were diagnosed maximum one month after diagnosis. At the same time, controls were selected from the patients who came to the same hospitals due to non-neoplastic, non-diabetic conditions including eye, gastrointestinal, ear, nose, and throat (ENT), kidney, and nerve diseases. Similar to the cases, the controls also did not follow any dietary regimens for chronic diseases. Cases and controls were matched for body mass index (<19, 19–25, 25–30, 30<kg/m2) and age (within strata of 5-year age groups). Total energy intakes of <800 or >4200 kcal/day and poor response to food frequency questionnaire considered as exclusion criteria. This research was approved by the ethic committee of Shiraz University of medical sciences and all participants provided informed consent (93-01-21-9059).

Demographic and Anthropometric Assessment

Demographic characteristics of participants including: smoking habit, physical activity level, ethnicity, job, education, and some medications usage were recorded using a general questionnaire via face to face interview. Weight was measured by a digital scale with a precision of 0.1 kg (Glamor BS-801, Hitachi, China), while individuals wore light clothing and no shoes. Height was measured at 0.1 cm precision in a standing position without shoes, using a non-stretchable tape. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Dietary intake assessment and estimation of dietary acid load

Dietary intakes were assessed using a semi-quantitative food frequency questionnaire (FFQ) (36-38). This questionnaire included 160 common food items which are common among Iranian population. Accordingly, the frequency of consumption of each food item was divided in nine categories: “never or less than once a month”, “1 to 3 times a month”, “once a week”, “2 to 4 times a week”, “5 to 6 times a week”, “once a day”, “2 to 3 times a day”, “4 to 5 times a day”, and “6 times or more a day”. In addition, the portions were classified in three sizes including: small (half of the defined average use or less), medium (equal to the defined average use), and large (one and half of the defined average use or more). The FFQs were analyzed using a specific multifunction software which developed by Borland Delphi 7 (http://www.embarcadero. com/products/delphi) and Visual Basic 2008 (VB 9.0) (http://www.microsoft.com/visualstudio/eng/ products/visual-studio-express-products). Daily intakes of energy, macronutrients, and micronutrients were derived using the Nutritionist 4 software. We used the PRAL and NEAP (indicators of dietary acid load) for estimation of dietary acid load. These indexes were calculated based on the previous published equation:

NEAP (mEq/day) = 54.5 × protein (g/day)/potassium (mEq/ day) - 10.2 [10]. PRAL (mEq/day) = 0.4888 x protein intake (g/day) + 0.0366 x phosphorus (mg/day) - 0.0205 x potassium (mg/day) - 0.0125 x calcium (mg/day) - 0.0263 x magnesium (mg/day)(39).

Statistical Analysis

The normality of the data was assessed using Kolmogorov-Smirnov test. Categorical variables presented as percent, and continuous variables presented as mean +- SD. One-way analysis of variance (ANOVA) test and Chi-square or Fischer exact tests were used for comparison quantitative and qualitative variables respectively, across tertiles of PRAL and NEAP scores. Dietary intakes of participants across tertiles of PRAL and NEAP scores were compared using analysis of covariance (ANCOVA) test and presented as mean +- SE. To assess risk of prostate cancer in relation to PRAL and NEAP, Multivariate logistic regression was used. In adjusted models, age, body mass index, energy intake, smoking, physical activity, ethnicity, job, education, and drug usage were controlled. Statistical analyses were performed using SPSS software (version 23, SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Results

Five participants (two cases and three controls) did not include in the analyses due to poor response to FFQ, and finally 120 participants (60 cases and 60 controls) included in final. The participant characteristics across the tertiles of PRAL and NEAP are shown in**Table 1** . It was observed that by increasing the score of PRAL, the BMI ($P = 0.03$) and physical activity ($P = 0.04$) of individuals decreased. Through tertiles of NEAP, the number of antihypertensive drug users were significantly increased ($P = 0.02$) and higher education level was associated with decreased NEAP score ($P = 0.04$). In addition, there was a direct association between the tertiles of both NEAP ($P =0.01$) and PRAL ($P = 0.003$) and the age of participants. **Table 2** presents the mean intake of food groups and nutrients across the tertiles of PRAL and NEAP. It shows that higher PRAL (P= <0.001) and NEAP (P= <0.001) scores were significantly associated with higher dietary protein intake. Moreover, higher PRAL and NEAP scores were significantly associated with greater vitamin B3 (PRAL; p= 0.003, NEAP; p= 0.002), vitamin B12 (PRAL; p= 0.001, NEAP; p= 0.001), zinc (PRAL; p= 0.01, NEAP; p= 0.01), grains (PRAL; p= 0.01, NEAP; p= 0.02), fish/poultry (PRAL; p= <0.001, NEAP; p= 0.002) and red/processed meats (PRAL; p= <0.001, NEAP; p= <0.001) intake. However, increased PRAL and NEAP scores were significantly associated with lower dietary fiber (PRAL; p= <0.001, NEAP; p= <0.001), vitamin A (PRAL; p= 0.01, NEAP; p= 0.04) , vitamin E (PRAL; p= <0.001, NEAP; p= <0.001), vitamin K (PRAL; p= <0.001, NEAP; p=<0.001), vitamin C (PRAL; p= <0.001, NEAP; p=<0.001), vitamin B6 (PRAL; p= 0.01, NEAP; p=0.02), vitamin B9 (PRAL; p= <0.001, NEAP; p= <0.001), potassium (PRAL; p= <0.001, NEAP; p=<0.001), calcium (PRAL; p= <0.001, NEAP; p=<0.001), magnesium (PRAL; p= <0.001, NEAP; p=<0.001), fruits (PRAL; p= <0.001, NEAP; p=<0.001) and vegetables (PRAL; p= <0.001, NEAP; p= <0.001). Additionally, higher NEAP score was linked with less total fat intake (p=<0.001) and higher PRAL score was associated with less intake of phosphorous (p= 0.04) and dairy (p= 0.21). The odds ratios (OR) of PC according to tertiles of PRAL and NEAP are presented in **Table 3** . Our crude results manifested that being in the third compared to the first tertiles of PRAL (OR=5.44; 95% CI= (2.09-14.17)) or NEAP (OR=4.88; 95% CI= (2.22-13.41)) increased the risk of PC. Moreover, after adjusting for potential confounders (energy intake, smoking, physical activity, ethnicity, job, education, anti-hyperlipidemic drugs, antihypertensive drugs, and aspirin), being in the third compared to the first tertiles of PRAL (OR=3.42; 95% CI= (1.11-8.65)) or NEAP (OR=3.88; 95% CI= (1.26-9.55)) was significantly associated with increased risk of PC.

Discussion

The results of this case-control study showed that dietary acid load assessed by both PRAL and NEAP, was significantly associated with the higher risk of PC. The association between some nutrients and risk of PC have been investigated previously (40-50). It seems that dietary intake is the largest external or environmental epigenetic factor capable of driving the development or maintenance of cancer (51). This study for the first time showed a positive association between DAL and risk of PC. In line with our findings,

some studies revealed that acidic environment and dietary acid load could contribute to cancer development. (35, 52-56). However, some other studies did not support these findings (35). Regarding to some specific types of cancer, previous research showed a significant positive association between net acid excretion and bladder cancer risk (57). In the other study, Yong-Moon Mark Park et al.(58) found higher risk of invasive and metastatic potential of breast cancer in relation to diet-dependent acid load in a nationwide large prospective cohort study (58). Besides, higher cancer mortality was associated with metabolic acid load, measured by lower serum bicarbonate (59). Mechanistically, some studies showed that carcinogenesis due to metabolic acidosis may occur through some intermediary effects (51). Metabolic acidosis, especially caused by dietary acid loads, can stimulate cancer metastasis, because of reduced buffering capacity of patients with cancer (60-63). Some studies on patients with cancer also showed changes in PH in the cancerous cells and their microenvironment, in such a way that intracellular pH (pHi) increased compared to normal cells (7.4 versus 7.2), while extracellular pH (pHe) decreased (6.7–7.1 versus 7.4) (64, 65). On the other hand, several studies have shown that different types of acid load interventions, such as dietary changes (66) or taking bicarbonate (67) or phosphate salt (68), could affect the pH of the urine, but not the pH of the blood. Generally, diet has potential to cause metabolic acidosis through affecting acid-base balance and producing acid or alkaline precursors (69-71), and consuming acidogenic diets could promote higher urinary acid excretion in comparison to alkalizing foods (72). Therefore, it seems that highlighting the roles of dietary acid load in relation to the cancer pathogenesis and performing most comprehensive studies to determine exact associations would be necessary.

This study had some strengths: First, this is the first study investigating the association between dietary acid load and risk of PC. Second, we used newly diagnosed cases to remove the effects of the patients' dietary intake changes on the cancer risk. Third, several confounders were adjusted in the statistical models which increase the possibility of the findings. Our study also had some limitations: First, however we used a validated semi-quantitate FFQ, response errors, recall bias, and social desirability are inevitable in gathering data using FFQ. Second, the probability of selection bias in case-control studies cannot be avoided and similar to all case–control studies, no cause and effect association could be interpreted between DAL and PC. Third, although we matched cases and controls by age and body mass index and adjusted the findings for several confounders, always there are some residual confounders, which might affect our findings.

In conclusion, the results of this study suggest that DAL could increase the risk of prostate cancer. However, further comprehensive prospective studies with larger sample size and longer duration are needed to confirm these findings.

Conflict of interest

The authors declare no conflict of interest.

Author Contribution:

Alireza Jafari and Seyed Amir Reza Mohajeri: data collection, Yahya Jalilpiran data analysis, Sanaz Mehranfar: manuscript writing, Shiva Faghih: supervising final manuscript.

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Table 1. General characteristics of participants across tertiles of PRAL and NEAP scores among 60 prostatic cancer cases and 60 hospital-based controls[a].

Variable
Age (y)
BMI (kg/m2)
Energy intake (Kcal/day)
Ethnicity
Fars
Non Fars
job
Employment
*Unemployment **
Education
Illiterate & primary
Diploma & academic
Smokers (%)
Physical activity
less or never
moderate
high
Antihyperlipidemic drug user(%)
Antihypertensive drug user(%)
Aspirin user (%)

PRAL, potential renal acid load; NEAP, net endogenous acid production; BMI, body mass index. ** Unemployed participa

Table 2. Dietary intakes of participants across tertiles of PRAL and NEAP scores among 60 prostatic cancer cases and 60 hospital-based controls.[a]

Variables	PRAL	PRAL	PRAL	PRAL	NEAP	NEAP	NEAP	NEAP
	Tertile 1 (N=40)	Tertile 2 (N=40)	Tertile 3 (N=40)	P-value[b]	Tertile 1 (N=40)	Tertile 2 (N=40)	Tertile 3 (N=40)	P-value
Carbohydrate (gr/day)	363.22 ± 13.87	316.94 ± 13.80	331.69 ± 13.71	0.06	362.87 ± 13.80	323.12 ± 13.74	325.86 ± 13.83	0.08
Protein (gr/day)	106.92 ± 3.07	104.56 ± 3.05	126.44 ± 3.03	<0.001	105.37 ± 3.08	106.66 ± 3.07	125.80 ± 3.09	<0.001
Total fat (gr/day)	60.12 ± 4.44	57.24 ± 4.42	68.30 ± 4.39	0.18	80.30 ± 4.35	54.88 ± 4.33	70.48 ± 4.36	0.04
Dietary fiber (gr/day)	27.96 ± 0.76	20.98 ± 0.75	18.96 ± 0.75	<0.001	27.67 ± 0.77	21.26 ± 0.77	18.98 ± 0.77	<0.001
Vitamin A (RAE/day)	3317.38 ± 206.04	2424.26 ± 205.01	3002.92 ± 203.70	0.01	3185.07 ± 207.16	2492.39 ± 206.17	3067.10 ± 207.56	0.04
Vitamin E (mg/day)	5.40 ± 0.20	4.05 ± 0.20	3.97 ± 0.20	<0.001	5.39 ± 0.20	4.09 ± 0.20	3.94 ± 0.20	<0.001

Variables	PRAL	PRAL	PRAL	PRAL	NEAP	NEAP	NEAP	NEAP
Vitamin K (µg/day)	152.70 ± 7.70	109.27 ± 7.66	109.83 ± 7.62	<0.001	150.75 ± 7.72	113.12 ± 7.68	107.93 ± 7.73	<0.001
Vitamin D (µg/day)	1.74 ± 0.37	1.56 ± 0.36	1.48 ± 0.36	0.88	1.75 ± 0.36	1.21 ± 0.36	1.83 ± 0.36	0.43
Vitamin C (mg/day)	221.67 ± 8.05	163.70 ± 8.01	135.23 ± 7.96	<0.001	220.62 ± 8.09	163.31 ± 8.05	136.67 ± 8.10	<0.001
Vitamin B1 (mg/day)	2.46 ± 0.08	2.29 ± 0.08	2.41 ± 0.08	0.29	2.45 ± 0.08	2.33 ± 0.08	2.38 ± 0.08	0.56
Vitamin B2 (mg/day)	2.32 ± 0.14	2.18 ± 0.14	2.74 ± 0.14	0.02	2.30 ± 0.14	2.24 ± 0.14	2.71 ± 0.14	0.05
Vitamin B3 (mg/day)	28.35 ± 1.10	28.66 ± 1.09	33.11 ± 1.08	0.003	28.14 ± 1.08	28.76 ± 1.08	33.23 ± 1.09	0.002
Vitamin B5 (mg/day)	7.06 ± 0.24	6.39 ± 0.24	7.17 ± 0.24	0.05	7.02 ± 0.24	6.50 ± 0.24	7.11 ± 0.24	0.15
Vitamin B6 (mg/day)	2.95 ± 0.18	2.27 ± 0.17	2.33 ± 0.17	0.01	2.93 ± 0.18	2.28 ± 0.17	2.34 ± 0.18	0.02
Vitamin B9 (µg/day)	401.88 ± 12.27	316.47 ± 12.21	317.08 ± 12.13	<0.001	397.63 ± 12.39	321.68 ± 12.32	316.12 ± 12.41	<0.001
Vitamin B12 (µg/day)	7.49 ± 2.60	8.75 ± 2.59	20.38 ± 2.57	0.001	6.85 ± 2.59	9.44 ± 2.57	20.32 ± 2.59	0.001
Potassium (mg/day)	5544.70 ± 154.99	4094.10 ± 154.21	3888.35 ± 153.23	<0.001	5493.94 ± 156.91	4160.38 ± 156.16	3865.63 ± 157.21	<0.001
Calcium (mg/day)	1280.50 ± 36.32	1051.64 ± 36.14	1063.23 ± 35.91	<0.001	1277.21 ± 36.06	1097.82 ± 35.89	1050.34 ± 36.13	<0.001
Iron (mg/day)	24.38 ± 1.51	22.67 ± 1.50	27.57 ± 1.49	0.06	23.69 ± 1.50	23.32 ± 1.49	27.61 ± 1.50	0.09
Magnesium (mg/day)	454.75 ± 12.46	358.39 ± 12.40	341.26 ± 12.32	<0.001	448.73 ± 12.71	364.13 ± 12.65	341.54 ± 12.74	<0.001
Zinc (mg/day)	11.81 ± 0.37	11.03 ± 0.37	12.63 ± 0.37	0.01	11.61 ± 0.37	11.16 ± 0.37	12.70 ± 0.37	0.01
Phosphorous (mg/day)	1511.73 ± 38.08	1379.47 ± 37.88	1476.19 ± 37.64	0.04	1502.47 ± 38.36	1410.48 ± 38.18	1454.43 ± 38.43	0.24
Fruits (gr/day)	637.78 ± 35.03	468.35 ± 34.39	345.34 ± 34.16	<0.001	639.18 ± 35.02	455.65 ± 34.39	356.67 ± 34.63	<0.001
Vegetables (gr/day)	812.68 ± 31.04	604.28 ± 30.89	548.17 ± 30.69	<0.001	800.50 ± 31.50	612.12 ± 31.35	552.51 ± 31.56	<0.001
Dairy (gr/day)	441.27 ± 25.33	400.38 ± 35.20	378.46 ± 25.04	0.21	451.44 ± 24.84	404.57 ± 24.72	364.10 ± 24.89	0.05

Variables	PRAL	PRAL	PRAL	PRAL	NEAP	NEAP	NEAP	NEAP
Nut/Legumes (gr/day)	56.34 ± 2.69	55.69 ± 2.68	51.57 ± 2.66	0.39	54.67 ± 2.65	58.23 ± 2.64	50.70 ± 2.66	0.14
Grains (gr/day)	367.97 ± 13.78	414.07 ± 13.71	429.46 ± 13.63	0.01	371.38 ± 13.81	416.23 ± 13.75	423.88 ± 13.84	0.02
Fish/Poultry (gr/day)	91.08 ± 7.51	99.50 ± 7.47	131.66 ± 7.43	<0.001	89.86 ± 7.57	104.48 ± 7.53	127.90 ± 7.58	0.002
Red/processed meats (gr/day)	65.38 ± 7.60	74.59 ± 7.56	112.80 ± 7.51	<0.001	61.30 ± 7.33	74.79 ± 7.29	116.67 ± 7.34	<0.001
PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]	PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]	PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]	PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]	PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]	PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]	PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]	PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]	PRAL, potential renal acid load; NEAP, net endogenous acid production. [a]
Data are presented as mean ± SE [b]	Data are presented as mean ± SE [b]	Data are presented as mean ± SE [b]	Data are presented as mean ± SE [b]	Data are presented as mean ± SE [b]	Data are presented as mean ± SE [b]	Data are presented as mean ± SE [b]	Data are presented as mean ± SE [b]	Data are presented as mean ± SE [b]
Ancova test was used	Ancova test was used	Ancova test was used	Ancova test was used	Ancova test was used	Ancova test was used	Ancova test was used	Ancova test was used	Ancova test was used

Table 3 . Risk of prostate cancer in relation to PRAL and NEAP among 60 prostatic cancer cases and 60 hospital-based controls[a].

Patterns
PRAL
No. cases/controls
Crude
Model 1
Model 2
Model 3
NEAP
No. cases/controls
Crude
Model 1
Model 2
Model 3

PRAL, potential renal acid load; NEAP, net endogenous acid production. [a] Multivariate logistic regression was used. Data

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and-risk-of-prostate-cancer-a-case-control-study