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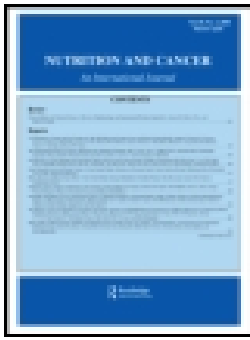
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Western Dietary Pattern, But not Mediterranean Dietary Pattern, Increases the Risk of Prostate Cancer

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ABSTRACT

Background and aim: Prostate cancer is the most common cancer among men. Several studies have investigated the effects of dietary patterns on prostate cancer risk, but this topic is still a matter of debate. This study aimed to examine the association between dietary patterns and prostate cancer risk.

Methods: In a case-control study, 60 newly diagnosed prostate cancer cases and 60 hospital-based controls were selected from two main hospitals of Shiraz, Iran. Data on dietary intakes, anthropometric features, and demographic characteristics were collected. To determine the dietary patterns factor analysis, and to estimate the odds ratios (ORs), multivariable logistic regression was performed.

Results: Two major dietary patterns were identified: Western dietary (WD) pattern and Mediterranean dietary (MD) pattern. After adjusting for potential confounders, men who had higher scores for WD pattern (above the median) were more likely to have prostate cancer (OR = 5.15; 95% CI (1.44–18.47); $P = 0.01$) compared with men who had lower scores. A nonsignificant inverse association was found for MD pattern (OR = 0.62; 95% CI (0.22–1.77); $P = 0.37$).

Conclusions: Our findings suggest that WD pattern may increase the risk of prostate cancer and the beneficial effects of MD pattern on prostate cancer risk need further research.

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Introduction

Prostate cancer is the most common cancer among males. It is also the second common cancer, after lung cancer, which is diagnosed in more than 1.1 million men globally (1). Nevertheless, in Iran prostate cancer is reported as the sixth most common cancer among general Iranian population and the third most common cancer among men, which was lower than the world level (2). Recent studies have reported that the incidence rate of prostate cancer is rising in Iranian population (3). In fact, age, ethnicity, positive family history of prostate cancer, and some genetic factors are the few established and not modifiable risk factors for the incidence of prostate cancer (4,5). Several studies showed that environmental and

dietary factors might also contribute to prostate carcinogenesis (6,7). Several epidemiological studies have reported reduced the risk of prostate cancer related to intake of carrots, coffee, and allium vegetables (8–10), whereas findings are controversial regarding the association between prostate cancer risk and intake of tea, fiber, tomato and lycopene (11–14), fat (15), fruits and vegetables (16), red meat, and processed meat, and seafood (17). It is also suggested that consumption of eggs, dairy products, and calcium may increase the risk of prostate cancer (17,18). However, based on World Cancer Research Fund International/American Institute for Cancer Research report, evidence on the role of certain nutrients and foods in the pathogenesis of prostate cancer is limited and controversial (19).

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Moreover, diets are composed of a variety of food items and nutrients; investigating the effects of individual nutrient or food does not reflect cumulative interactions among them (20,21). To overcome these limitations, several studies have investigated the effect of dietary patterns on prostate cancer risk over the past decade (22–28). Despite several studies addressing the association between dietary patterns and prostate cancer risk, the issue is still open for discussion. In addition, studies examining this association in Middle Eastern countries are scarce, and no study has been performed in this region on newly diagnosed patients. Therefore, this study was carried out to investigate the association of dietary patterns and risk of prostate cancer in newly diagnosed prostate cancer patients in Shiraz-Iran.

Materials and Methods

Participants

From April to September 2015, 125 subjects (62 cases and 63 hospital-based controls) participated in a case-control study in Shiraz, Iran. Both cases and controls were selected from two main hospitals that are the referral centers of urology disorders in Shiraz, Iran. Patient' medical records were obtained from cancer registry database of the hospitals, the biggest and the most referred medical centers for other provinces in the southern part of Iran for all types of diseases, including cancer (29,30). Demographic and dietary intakes were collected by face-to-face interview and anthropometric indices were measured.

The cases were newly diagnosed prostate cancer patients (maximum 1 mo after diagnosis) whose disease was histologically confirmed by a pathologist and they were candidate for radical or open prostatectomy. They did not have any history of dietary regimens for chronic diseases, diabetes, or cancers of other sites. At the same time, controls were selected from patients that visited the same hospitals due to nonneoplastic, nondiabetes conditions including eye ($n=21$), ear, nose, and throat (ENT) ($n=20$), kidney ($n=8$), nerve ($n=5$), and gastrointestinal ($n=9$) diseases. Similar to the cases, the controls also did not follow any dietary regimens for chronic diseases. Cases and controls were frequency matched by body mass index (<19 , $19-25$, $25-30$, $30 < \text{kg/m}^2$) and age (within strata of 5-year age groups). As matching was carried out by age in this case-control study, controlling for it in the analysis must be considered and we performed logistic regression analyses in order to reduce the chance of residual confounders (31). Total energy intake of <800 or >4200 kcal/day and poor response to food frequency questionnaire

(FFQ) (do not respond to >70 items of 160 items) were considered as exclusion criteria (32).

Demographic and Anthropometric Assessment

Lifestyle and demographic information were collected using a questionnaire that included questions on smoking (smokers/nonsmokers), ethnicity (Fars/Non Fars), job (employment/unemployment), education (illiterate & primary/diploma & academic), physical activity (little or never/moderate/high), and some medications (antihyperlipidemic drugs, antihypertensive drugs, and aspirin) (yes/no). Also, height and weight were measured at the time of interview and BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Weight was measured by a digital scale in light clothing to the nearest 0.1 kg (Glamor BS-801, Hitachi, China), and height was recorded using a nonstretchable tape measure without shoes to the nearest 0.1 cm.

Dietary Intake Assessment

Dietary intake was assessed using a valid and reliable semi-quantitative FFQ that represent the usual intakes of the patients (33,34). Briefly, this questionnaire consists of 160 food items, determined based on common average portion sizes within the Iranian population. In order to determine the frequency of each food item consumption, nine categories were defined: “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”. Also, for classifying the portions, three sizes were defined as 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). In order to analyze the completed FFQs and reduce the risk of error during recording, a specific multifunction software was developed. First, all pages of the FFQs were scanned (HP Scanjet N8420 scanner, CA, USA) and imported to the software. The first part of the software read the selected choices on the scanned pages of the FFQs and delivered them as an external file with TXT format. This part of the software was programed by Borland Delphi 7 (<http://www.embarcadero.com/products/delphi>). Then, the second part of the software analyzed the data derived from the first part and exported the data to an SPSS file. This part of the software was programed by Visual Basic 2008 (VB 9.0) (<http://www.microsoft.com/visualstudio/eng/>

products/visual-studio-express-products). In the software, the amount of energy per 100 g of food items was defined according to the food composition tables (35). Then, all food items were categorized into 20 food groups based on the similarity of nutrients or culinary usage of foods (36).

Statistical Analysis

Principal component factor analysis with varimax rotation was performed on 20 food groups for detecting the dietary patterns. Two factors with eigenvalues >1, rotated factor loading greater than 0.1, and a clear inflexion in the scree plot were other options selected for doing factor analysis.

Factor scores for each participant and each dietary pattern were calculated by adding the intake from each of the food groups weighted by factor loading. Factor loadings indicate the power of the correlation coefficients between dietary patterns and food groups. A negative loading reveals an inverse, and a positive loading indicates a direct association.

Based on the median, factor scores were categorized into two categories for the participants (the first category was under the median (references), and the second one was equal or above the median). Then, the associations between dietary patterns and prostate cancer risk were evaluated through multiple logistic

regression with adjustments for potential confounders, such as: age (model 1), age plus body mass index and total energy intake (model 2), and previous variables plus physical activity, smoking, job, education, and some drugs usage (antihyperlipidemic drugs, antihypertensive drugs, and aspirin) (model 3). Relationships between quantitative variables across groups (cases and controls) and quantitative variables across categories of each dietary pattern scores were assessed using independent T-test or Mann–Whitney test. Also, Chi-square test or Fisher's exact test were used to assess the distribution of the participants between cases and controls in terms of categorical variables. Data were analyzed using SPSS version 22.0 software (IBM, Armonk, NY) and Statistical analysis was conducted assuming two-sided 5% level of significance and a *P* value of <0.05 was considered significant in the statistical analyses.

Results

Two cases and three controls were excluded from the study due to poor response to FFQ, and the final sample included 60 cases and 60 controls (response rate = 96%).

Characteristics of the cases and controls by demographic and anthropometric factors and energy intake are summarized in Table 1. The mean [\pm SD] age for

Table 1. Associations between prostate cancer and sociodemographic characteristics, anthropometric measures, and energy intakes among 60 cases and 60 controls, Iran, April–September 2015.

Variables*	Case	Control	<i>P</i> value
Age (year) (n%)			0.21
<60	7 (11.7)	8 (13.3)	
60–65	18 (30.0)	27 (45.0)	
65–70	24 (40.0)	14 (23.3)	
≥70	11 (18.3)	11 (18.4)	
BMI [‡]	24.84 ± 3.64	25.85 ± 3.46	0.12
Total energy intake (kcal/day)	2712.24 ± 593.48	2596.10 ± 712.77	0.33
Ethnicity			0.65
Fars	48 (80)	46 (77)	
Nonfars	12 (20)	14 (23)	
Job			0.57
Employment	34 (57)	37 (62)	
Unemployment**	26 (43)	23 (38)	
Smokers (%)	14 (23)	16 (27)	0.67
Education			0.09
Illiterate and primary	41 (68)	32 (53)	
Diploma and academic	19 (32)	28 (47)	
Physical activity			0.02
Little or never	23 (38)	12 (20)	
Moderate	25 (42)	24 (40)	
High	12 (20)	24 (40)	
Antihyperlipidemic drug user (%)	6 (11)	6 (11)	1.00
Antihypertensive drug user (%)	19 (32)	13 (22)	0.21
Aspirin user (%)	10 (17)	15 (25)	0.26

*Data are presented as mean \pm standard deviation or number (%).

**Unemployed participants were retired or jobless individuals.

[‡]BMI: body mass index

Independent sample *t*-test or Mann–Whitney U-test was used for comparison of quantitative variables and Chi-square test or Fisher's exact test was used for comparison of qualitative variables.

Table 2. Food groups used in the factor analysis and factor loadings for each of the identified dietary patterns among 60 cases and 60 controls, Iran, April–September 2015.

Food groups	Food items	MD pattern	WD pattern
Sweets and desserts	Cookies, cakes, muffins, pies, pancake, sugar, jam, honey, candies, chocolate, sweet tahini, others	0.12	0.51
Red and processed meats	Beef and veal, sheep, lamb, minced meat, hamburger, sausages	0.10	0.67
Poultry	Chicken, turkey, ostrich	0.10	0.40
Fish	All fish types	0.39	–
Organ meats	Liver, kidney, heart, offal, rennet, tongue, brain	–	0.51
Salty snacks	Potato chips, popcorn, biscuits, crackers, others	–	0.21
Tea and coffee	Tea, bitter coffee, sweet coffee	–	0.46
Soft drinks	Soft drinks	–0.14	0.62
Pickles	Salty Cucumbers, sauerkraut, and other pickles	0.14	0.30
Fruit, fruit juices	All fruit types, natural fruit juices, artificial fruit juice and canned fruits	0.75	–
Nonstarchy vegetable	Broccoli, cabbage, cauliflower, kale, carrot, garlic, tomato, lettuce, spinach, cucumber, eggplant, onion, green beans, squash, mushroom, pepper, vegetables water, others	0.74	–
Starchy vegetables	Legumes, potato, peas	–	0.66
Egg	egg	–0.21	0.44
Whole grains	Whole-wheat breads (e.g., barbari, sangak, taftun), barley bread, barley	0.10	–0.11
Refined grains	White breads, rice, pasta, noodle	–	0.37
Low-fat dairy	Low-fat milk and yogurt, cheese, kashk, dough	0.33	0.20
High-fat dairy	High-fat milk, high-fat yogurt, cream cheese, cream, ice cream, others	0.23	0.36
Hydrogenated fats	Solid fats (animal origin), animal butter, margarine, hydrogenated vegetable oils	–	0.47
Olive	Olive	0.60	–
Nuts	All nuts (almonds, hazelnut, seeds, peanut, walnut, pistachio, others)	0.67	–0.15
Explained variance (%)	–	11.99	15.67

Table 3. Participants' characteristics according to different categories of the dietary patterns among 60 cases and 60 controls, Iran, April–September 2015.

Variables	WD pattern			MD pattern		
	Category ₁	Category ₂	<i>P</i> value	Category ₁	Category ₂	<i>P</i> value
Age (year) (<i>n</i> %)			0.82			0.74
<60	8 (13.3)	7 (11.7)		8 (13.3)	7 (11.7)	
60–65	23 (38.4)	22 (36.6)		22 (36.7)	23 (38.3)	
65–70	20 (33.3)	18 (30.0)		17 (28.3)	21 (35.0)	
≥70	9 (15.0)	13 (21.7)		13 (21.7)	9 (15.0)	
Total energy (kcal/day)	2215.81 ± 433.55	3092.53 ± 536.95	<0.001	2406.67 ± 597.18	2901.67 ± 621.22	<0.001
BMI	25.19 ± 3.60	25.50 ± 3.56	0.64	24.56 ± 3.62	26.13 ± 3.37	0.01
Cases (%)	22 (36.7)	38 (63.3)	0.003	34 (56.7)	26 (43.3)	0.14
Unemployment** (%)	30 (61.2)	19 (38.8)	0.04	18 (36.7)	31 (63.3)	0.01
Smokers (%)	8 (26.7)	22 (73.3)	0.003	12 (40.0)	18 (60.0)	0.20
Illiterate & primary (%)	33 (45.4)	40 (54.8)	0.19	44 (60.3)	29 (39.7)	0.005
Physical activity (less or never) (%)	10 (28.6)	25 (71.4)	0.01	19 (54.3)	16 (45.7)	0.28
Antihyperlipidemic drug user (%)	5 (41.7)	7 (58.3)	0.54	2 (16.7)	10 (83.3)	0.01
Antihypertensive drug user (%)	17 (53.1)	15 (46.9)	0.68	14 (43.8)	18 (56.3)	0.40
Aspirin user (%)	13 (52.0)	12 (48.0)	0.82	8 (32.0)	17 (68.0)	0.04

Dietary pattern scores have been categorized according to the median (60 subjects in each category).

Data are presented as mean ± standard deviation or number (%). Category 1: under the median, Category 2: equal or above the median.

Independent sample *t*-test or Mann–Whitney *U*-test was used for comparison of quantitative variables.

Chi-square test or Fisher's exact test were used for comparison of qualitative variables.

**Retired or jobless individuals.

cases and controls was 66.0 [±9.6] and 61.4 [±9.4], respectively. Physical activity level was significantly ($P=0.02$) higher in the controls than cases.

As shown in Table 2, two dietary patterns were derived from factor analysis on 20 food groups. The dietary pattern characterized by high amount of sweets and desserts, red and processed meats, poultry, organ meats, salty snacks, tea and coffee, soft drinks, pickles, starchy vegetables, eggs, refined cereals, high-fat dairy, and hydrogenated fats was identified as western dietary (WD) pattern. The dietary pattern characterized by high amount of fish, fruit and fruit juices, nonstarchy vegetables, nonrefined cereals, low-fat dairy, olive, and nuts

was identified as a Mediterranean dietary (MD) pattern. In total, both dietary patterns account for 28% of the variance in the food groups.

Participants' characteristics according to different categories of the dietary patterns are shown in Table 3. Compared to those in the lower category of WD pattern (below median), participants in the higher category had a higher total energy intake ($P<0.001$). Moreover, a greater proportion of participants in the higher category reported being a smoker ($P=0.003$), higher physical activity (moderate & high vs. less or never) ($P=0.01$), being employed ($P=0.04$), and being a prostate cancer patient

Table 4. Risk of prostate cancer in relation to identified dietary patterns among 60 cases and 60 controls, Iran, April–September 2015.

Dietary pattern	Risk of prostate cancer			
	Crude	Model 1	Model 2	Model 3
WD pattern				
Category 1 (ref)	1	1	1	1
Category 2	3.58 (1.62–7.87)	3.95 (1.73–9.00)	4.83 (1.62 – 14.40)	5.15 (1.44– 18.47)
<i>P</i> value	0.002	0.001	0.005	0.01
MD pattern				
Category 1 (ref)	1	1	1	1
Category 2	0.44 (0.20–0.97)	0.51 (0.22–1.15)	0.58 (0.24–1.44)	0.62 (0.22– 1.77)
<i>P</i> value	0.04	0.10	0.24	0.37

Data are presented as adjusted odds ratios and 95 % confidence intervals.

Dietary pattern scores were categorized according to the medians.

Model 1 was adjusted for age.

Model 2 was adjusted for age plus body mass index and total energy intake.

Model 3 was adjusted for confounders in model 2 plus physical activity, smoking, job, education, and some drug usage (antihyperlipidemic drugs, antihypertensive drugs, and aspirin).

($P=0.003$). Compared with lower category, those in the higher category of MD pattern, had higher BMI ($P=0.01$), total energy intake ($P<0.001$), education status ($P=0.005$), antihyperlipidemic medication ($P=0.01$), and aspirin usage ($P=0.04$). In contrast with WD pattern, unemployment in the higher category of MD pattern was compared to those in the lower category ($P=0.01$). Statistical differences for other results were not significant.

Adjusted odds ratios (ORs) and 95% Confidence Intervals (CIs) for the risk of prostate cancer associated with the two identified dietary patterns are presented in Table 4. In pooled data analysis, those in the second category of MD pattern had a significantly lower risk of prostate cancer compared with patients in the first category (OR=0.44; 95% CI (0.20–0.97); $P=0.04$). Moreover, those in the second category of WD pattern had a significantly higher risk of prostate cancer compared with patients in the first category (OR=3.58; 95%CI (1.62–7.87); $P=0.002$).

After adjusting for potential confounders, compared with the first category of MD pattern, being in the second category was not associated with prostate cancer risk (OR=0.62; 95% CI (0.22–1.77); $P=0.37$). However, the association between the second category of WD pattern and a higher risk of prostate cancer remained significant (OR=5.15; 95% CI (1.44–18.47); $P=0.01$).

Discussion

This study, two major dietary patterns were identified, of which the WD pattern was significantly associated with higher risk of prostate cancer.

The identified WD pattern in this study approximately resembled the Western patterns identified by three other studies (26,37,38). Positive association

of this dietary pattern with prostate cancer risk was seen in two studies (26,37), but not all (38). In some other studies, different dietary patterns including processed (39), western (24), refined carbohydrate (25), starch-rich (40), and traditional (27) patterns were significantly associated with an increased risk of prostate cancer. Besides, in some studies, traditional Western (39), and Western (41) patterns were associated with a nonsignificant increased risk of prostate cancer. Interestingly, almost all components of these patterns were part of our identified Western dietary (WD) pattern, which was significantly associated with an increased risk of prostate cancer.

Furthermore, in a nutrient-based dietary pattern study (40), animal products pattern which includes animal protein, calcium, saturated fatty acids, phosphorus, riboflavin, cholesterol, milk and dairy products, zinc, cheese, eggs, and red meat increased the risk of prostate cancer. Additionally, a new systematic review and meta-analysis study on the relationship between different dietary patterns and prostate cancer risk, which included 12 observational studies found a significant linear trend between WD pattern and increment of prostate cancer risk (42).

The WD pattern identified in our study was high in egg and high-fat dairy foods, which are suggested to be associated with an increased risk of prostate cancer (17,18). Other components of WD dietary pattern, such as processed meat and red meat are recently reported as “carcinogenic and probably carcinogenic to humans” by the International Agency for Research on Cancer (IARC) classifications (43). Besides, carbohydrate-rich foods of WD dietary pattern, such as sweets and desserts, soft drinks, starchy vegetables and refined grains with high glycemic index values are associated with an increased risk of insulin resistance and hyperinsulinemia (44). It is suggested that long-term

hyperinsulinemia may increase the risk of cancer through stimulating the signaling pathways that promote tumor development and progression (45).

The MD pattern in our study was significantly associated with reduced risk of prostate cancer in the crude analysis. However, the association became non-significant after adjusting for potential confounders, which might be due to a lack of power in our study. In a cohort study by Jackson et al., no association was found between the MD pattern and prostate cancer risk (23). Besides, in other studies, different dietary patterns including fruit and salad (22), vegetable (22,26), vegetable-fruit (46), prudent (24,27,41), and healthy living (39) patterns were also not associated with prostate cancer risk. In contrast, in a systematic review and meta-analysis of 56 observational studies, the greatest adherence score to Mediterranean diet was significantly associated with a lower risk of prostate cancer (47).

Also in the other cohort (48) and case-control (49,50) studies, adherence to a modified Mediterranean diet score was not associated with prostate cancer risk. In contrast, Askari et al. found that greater adherence to Mediterranean-diet is associated with reduced the risk of prostate cancer (51). As mentioned above, there is no consistent agreement on the protective effect of Mediterranean diet in relation to prostate cancer risk, so further studies are needed in this context.

Mediterranean diet is high in fruits and vegetables which contain trace minerals, vitamins, fiber, and other biologically active components, with the antioxidant activity which protects human body's cells against DNA, RNA, and lipids and proteins damages (52). Also, fish, as a rich source of long-chain polyunsaturated fatty acids, has some preventive roles in carcinogenesis including the effect on some transcription factors activity, signal transduction, and gene expression pathways and also improvement of insulin sensitivity and suppression of arachidonic-acid-derived eicosanoid biosynthesis which is associated with inflammation and carcinogenesis (53). Furthermore, olive and olive oil are other constituents of MD pattern. They contain oleic acid which regulates cancer-related oncogenes (54). Several studies also demonstrated that phenolic compounds of olive and olive oil induce apoptotic cell deaths (55,56) and also have antiinflammatory and DNA oxidation-reduction effects which are involved in human carcinogenesis (55,57). As another component of MD pattern, nuts are also rich in bioactive compounds involved in angiogenesis, and cell invasion, survival, and proliferation (58).

We also found that some characteristics of participants were different according to the type of each dietary pattern. WD pattern was inversely related to physical activity and unemployment. However, this pattern was positively associated with total energy intake and smoking. Our findings of the associations of smoking and physical activity with WD pattern are in line with some other studies (26,59,60) which showed that higher adherence to WD pattern was related to a greater proportion of smokers and a lower proportion of physically active men. The positive association between WD pattern and smoking might be confounded by coffee consumption since both WD pattern and smoking are associated with high coffee consumption (61–63). In concordance with our findings, WD pattern was positively associated with total energy intake in a cohort (60) and two case-control (24,39) studies. On the other hand, our findings showed that MD pattern was positively associated with total energy intake, BMI, unemployment, educational status and antihyperlipidemic, and antihypertensive drug usage. The positive association between MD score and a healthy living pattern (rich in poultry, fish, whole grains, cereals, fruit, and all vegetable) with education status was found in previous studies (39,64). However, the association between MD and total energy intake and BMI showed inconsistent results in previous studies; the inverse (65) and no (48,66–68) associations between this pattern and the total energy intake, BMI, or both of them were found in some studies. Nevertheless, other studies reported a positive association between MD score and a healthy living pattern (rich in poultry, fish, whole grains, cereals, fruit, and all vegetable) and total energy intake (39,64). Besides, greater adherence to the Mediterranean-type dietary pattern in Iranian adults was shown to be associated with an increased energy intake (69).

Our study has several strengths. First, to the best of our knowledge, this is the first study investigating the association between dietary pattern and prostate cancer risk in newly diagnosed prostate cancer patients (which minimize recall bias) in Middle Eastern male population. Second, the similarity between the identified dietary patterns in our study with dietary patterns in other studies made the comparisons of results easier. Third, information on most of demographic and lifestyle confounders involved in prostate cancer pathogenesis was collected and adjusted in the analyses to make the results less prone to bias. Fourth, our data were collected from

two main hospitals as the referral centers for urology disorders, and we did not have any missing in the data.

Our study also had some limitations: 1) although we used a validated semi-quantitate FFQ to minimize measurement error, using FFQ is one of the problems associated with dietary pattern assessment; 2) Small sample size which might be affect our findings is another limitation; 3) Besides, although we selected the cases and controls from the same hospitals, the selection bias in case-control studies cannot be neglected. We also had no information about the stage and grade of the disease, though we selected the cases who were candidate for radical or open prostatectomy.

In conclusion, the results of this study suggest that a WD pattern may increase the risk of prostate cancer and the beneficial effects of MD pattern on prostate cancer risk need further research.

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Disclosure Statement

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