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Adherence to Mediterranean-Style Dietary Pattern and Risk of Prostate Cancer: A Case-Control Study in Iran

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Abstract: It has been well established that the incidence of PCa is lower in people living in the Mediterranean region compared to Western societies. This condition might be related to traditional Mediterranean Diet (MD) which has been used by this population. Recent reports have examined the MD on the risk of PCa, but the results are inconsistent. The purpose of the present study was to examine the relationship between adherence to MD and PCa risk in case-control study of Iranian men. The present study was conducted in Tehran (capital of Iran). Cases were cancer patients aged 40-78 years with incident, histologically confirmed PCa diagnosed not before 6 months of the interview. Controls were patients (43-71 years) who were sampled randomly from patients admitted to the same hospital as cases during the same time period (for acute, non-neoplastic conditions and not afflicted with diet-related chronic diseases). In total, 52 patients with PCa and 104 controls underwent face-to-face interviews by specifically trained professional interviewers (participation rate: 85%). We retrospectively assessed the association between MD and PCa in a population-based case-control study. Adherence to MD was associated with reduced risk of PCa. We found an inverse association between vegetables, fruits, dairy, fish, olives, legumes and nuts consumption with PCa risk.

Key words: Prostate cancer, mediterranean diet, case-control study

INTRODUCTION

It's well known that prostate cancer (PCa) is the most prevalent cancer among males worldwide (Jemal *et al*., 2011). In 2011, PCa constituted about 29% of all cancer diagnoses and 11% of all deaths from cancer in men (Siegel *et al*., 2011). PCa has an incidence of 9.6 per 100,000 (ranging from 3.2 to 16.0 per 100,000 according to different geographical setting) in Iran (Sadjadi *et al*., 2007). This is close to Asia-Pacific region (9.9 per 100,000) but much lower than the world (32.8 per 100,000) (Sadjadi *et al*., 2007).

It has been well established that the incidence of PCa is lower in people living in the Mediterranean region compared to Western societies (Itsiopoulos *et al*., 2009). This condition might be related to traditional Mediterranean Diet (MD) which has been used by this population (Pauwels, 2011). MD has drawna great deal of attention with the prevention of chronic diseases such as Cardiovascular disease (CVD), cancers, type 2 diabetes and some neurodegenerative diseases (Roman *et al*., 2008; Sofi *et al*., 2010). The traditional MD is generally characterized, despite regional disparities, by abundant use of whole grains, fruits, vegetables, low fat dairy, nuts, poultry, legumes, lean fish, small quantities of red meat, moderate alcohol consumption and olive oil as the main source of dietary fat (Keys *et al*., 1986; Simopoulos, 2001; Trichopoulou *et al*., 2000; Willett, 2006; Tyrovolas and Panagiotakos, 2010).

Anti-inflammatory properties of diet include lipophilic component of fruit, alpha-tocopherol and phenolic compounds. Phenolic compounds (Resveratrol, quercetin and catechin) which are found in red wine, grape skin, peanuts, raisins and blackberries, have the ability to affect cell proliferation, cell cycle progression and apoptosis in cancer cells (Nelson *et al*., 2003; Corona *et al*., 2009; Ferris-Tortajada *et al*., 2012). Moreover a large amount of fiber which is used in MD is associated with a lower risk of cancer (Koushik *et al*., 2007; Wiseman, 2008).

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Recent reports have examined the MD on the risk of PCa, but the results are inconsistent (Kontou *et al*., 2011). Moreover there is a lack of published data in developing countries on this issue. Before any firm conclusion can be drawn, more results from developing countries are required. Epidemiological studies in these countries could substantiate the existing evidence, as well as to provide valuable new information.

The purpose of the present study was to examine the relationship between adherence to MD and PCa risk in case-control study of Iranian men.

MATERIALS AND METHODS

Study population: The present study was conducted in Tehran (capital of Iran). Cases were cancer patients aged 40-78 years who were admitted to 'Labbafi-Nejad Hospital' with incident, histologically confirmed PCa diagnosed not before 6 months of the interview. Controls were patients (43-71 years) who were sampled randomly from patients admitted to the same hospital as cases during the same time period (for acute, non-neoplastic conditions and not afflicted with diet-related chronic diseases). Thus we included a range of control diagnosis (eye or nose disorders, skin diseases, fractures and sprains, trauma and injuries and other illnesses e.g., removal of plates, pins, screws and wires). Cases and controls were frequency matched according to age (5-year groups) and body mass index (<19, 19-25, 25-30, 30<). In total, 52 patients with PCa and 104 controls underwent face-to-face interviews by specifically trained professional interviewers (participation rate: 85%). We excluded 5 subjects due to poor responses with regard to dietary questions (with more than 95 missing food items in the questionnaire). Moreover, we excluded one patients from the analysis because their log scales of total energy intake was >3 SD from the mean, indicating errors in their responses to the dietary questions. In addition, a control subject who did not report any information on all 13 elements in the Mediterranean food pyramid was excluded. After exclusions, the data included 50 cases with PCa and 99 controls.

Assessment of dietary intake: Dietary intake was assessed with the use of an administered food-frequency questionnaire (FFQ) that included 168 food items commonly consumed in Iran. This reliable and valid FFQ (Esfahani *et al*., 2010) consists of 168 food items with standard serving sizes and subjects were asked to report their intake frequency for each food item on a daily, weekly, monthly or yearly basis. These reported consumptions were then converted to daily frequencies and the manual for household measures was used to convert intake frequencies to daily grams of food intake (Ghaffarpour *et al*., 1999). Food energy value was based on the Nutrients Composition of Iranian Foods (NCIF) and the USDA Food Composition Data (Safari *et al*., 2013). The latter was used for foods or food ingredients that were not available in NCIF.

Assessment of non-dietary exposures: Using a general questionnaires we collected participants' socio demographic and lifestyle information including family history of cancer (yes/no), age (years), having diabetes (yes/no), current smoking (yes/no) and ethnicity (Fars, not Fars).Waist circumference was assessed at the slimmest part, using a tape and was recorded to the nearest 0.1 cm. Weight and height were evaluated while participants were wearing only light clothing without shoes. Height was evaluated using a stadiometer (Seca 214 portable stadiometer) and was recorded to the nearest 0.1 cm. Weight was measured by using digital scales (Seca 881, Germany) and it was recorded to the nearest 0.1 kg. Body mass index (BMI) was then computed by dividing the weight in kg by square of height in meters.

Mediterranean style dietary pattern: In the present study, adherence to MD were scored using MSDPS (Mediterranean-style dietary pattern score) which has 13 elements that reflects the 13 food groups in the Mediterranean food pyramid. These food groups listed as; whole-grain cereals, fruits, vegetables, dairy products, wine, fish and other seafood, poultry, olives/legumes/nuts, potatoes and other starchy roots, eggs, sweets, meat and olive oil (Rumawas *et al*., 2009). The present study confined on 12 food groups since participants were reluctant to answer the questions which related to their alcohol consumption because of their religious beliefs (Hosseini-Esfahani *et al*., 2010). According to the food guide pyramid recommendation, for each food group, the number of daily or weekly servings is recommended which each person is expected to consume. With the exception of olive oil group, each food group is scored 0-10 according to the degree of individuals' adherence to each recommendation and a penalty was appointed that was proportional to the number of servings consumed over the pyramid recommendations (Rumawas *et al*., 2009). Zero score was allocated to individuals whose total score or MSDPS was negative due to the over consumption penalty. Olive oil is scored in a different way categorically, so that exclusive olive oil intake resulted in obtaining a score of 10, use of olive oil along with other vegetable oils scored 5 and no olive oil intake was scored 0 (Rumawas *et al*., 2009). Then, the 12 component scores were summed in order to calculate the total MSDPS that standardized to a 0 (minimal adherence to the traditional Mediterranean diet) to 100 (maximal adherence), we used the following equation (Rumawas *et al*., 2009):

$$MSDPS = \frac{\sum_{i=1}^{12} si}{[(120)\times 100]\times p}$$

where, Si is the individual item score and p, is the proportion of total energy intake from Mediterranean diet pyramid foods.

Statistical analysis: MSDPS was normally distributed and was divided into tertile categories of exposure according to the control distribution. The intake of Mediterranean food groups by PCa cases and controls were compared using an independent sample t test. Spearman correlation coefficients were calculated to assess the association between individual MSDPS components and the total score. Analysis of covariance was run to compare characteristics of participants across the tertile categories of MSDPS for cases and controls separately. For ordinal variables, chi-square test or Fisher's exact test and for continuous variables, Mann-Whitney test or Student t test, were applied to compare case and control groups. To detect the p value for trend, the linear regression coefficient for continuous variables and binary logistic regression coefficient for the dichotomous variables for the MSDPS were used. To evaluate the independence of the relationship between PCa risk and MSDPS, adjusted odds ratios (ORs) were measured using the multiple logistic regression with the lowest MSDPStertile as the reference category. Potential confounders were included in the multivariate models based on the review of literature, comparison of cases and controls and whether they modified the risk estimates 10% or more.

Tests for trends were performed by treating the categorical variables as continuous predictors in the logistic regression models. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS v. 14, Chicago, IL). All the reported P-values are two-sided.

RESULTS

Table 1 shows the characteristics of 50 cases of prostate cancer and 99 controls according to the selected variables. Cases had higher family history of cancer, smoking usage and diabetes.

Table 2 shows dietary intake, score distribution and spearman rank correlation of MSDPS in both cases and controls. According to the Table 2, compared to the controls, cases had lower intake of protective Mediterranean diet component (fruits, vegetables, dairy, fish and other seafood, olives, legumes, nuts and olive oil) and higher intake of whole grains, poultry, potato and other starchy roots, eggs, sweets and meat.

Table 3 shows the characteristics of participants according to the MSDPS tertile categories. We could not detect any significant association between characteristics of subjects and MSDPS in both cases and controls.

Table 1: Characteristics of Iranian Men in a Case-Control study of prostate cancer in 2011 to 2012

	Control	Prostate cancer
Number	99	50
Age (Mean, Years)	54.80 (6.02)*	57.40 (5.90)*
BMI (Mean, kg/m^2)	25.08 (3.65)*	27.82 (4.46)*
Waist Circumstance (Mean, Cm)	95.85 (1.02)*	105.72 (8.29)*
Ethnicity (n, %)		
Fars	89 (90)	41 (82)
Not Fars	10 (10)	9 (18)
Smoking (n, %)		
Yes	5 (5)	23 (46)
No	94 (95)	27 (54)
Family history of cancer (n, %)		
Yes	13 (13)	14 (28)
No	86 (87)	36 (72)
Diabetes (n, %)		
Yes	7 (7)	13 (26)
No	92 (93)	37 (74)

*indicates mean (SD)

In Table 4, odds ratio (OR) of prostate cancer and the corresponding 95% confidence interval (CI) across the tertiles of MDS are presented. In age adjusted model, the OR of prostate cancer decreased in the third as compared to the first tertile of MDS (age adjusted OR: 0.22, 95% CI: 0.08-0.58; p-trend: 0.001), multivariate adjusted OR in the third tertile increased slightly compared to the second tertile (OR: 0.22, 95% CI: 0.07-0.75; p-trend: 0.005).

In Table 5, adjusted ORs and 95% CIs for PCa by component of MSDPS are shown. Comparing subjects over the median value of each component to those below the median, higher consumption of fruits (OR = 0.29, 95% CI: 0.11-0.78), vegetables (OR = 0.03, 95% CI: 0.00-0.16), dairy (OR = 0.08, 95% CI: 0.02-0.29), fish and other sea food (OR = 0.06, 95% CI: 0.01-0.26), olives, legumes and nuts (OR = 0.03, 95% CI: 0.00-0.19) were significantly associated with reduced PCa risk. In contrary high consumption of potatoes and other starchy roots (OR = 7.30, 95% CI: 2.19-24.26), eggs (OR = 10.69, 95% CI: 1.48-77.02), sweets (OR = 7.65, 95% CI: 2.39-24.46) and meat (OR = 3.40, 95% CI: 1.20-9.62) increased the risk of PCa.

DISCUSSION

We retrospectively assessed the association between MD and PCa in a population-based case-control study. Adherence to MD was associated with reduced risk of PCa. We found an inverse association between vegetables, fruits, dairy, fish, olives, legumes and nuts consumption with PCa risk.

The results of our study is in agreement with results reported in recent systematic review and meta-analysis of observational studies (Schwingshackl and Hoffmann, 2014). After meta-analysis of 21 cohort studies and 12 case-control studies, they showed that high adherence to a MD is associated with a significant reduction in the risk of prostate cancer (4%). Using MD patterns in Asians, American and Nordic populations might not completely represent conformity with the traditional MD

Table 2: Dietary intakes, score distribution and spearman rank Correlation of the mediterranean-style dietary pattern score (MSDPS) in an Iranian case-control study of prostate cancer, 2011-2012

	Prostate cases			Controls		
Food groups	Intake distribution[1]	Score distribution[1]	Spear RC to total MSDPS[2]	Intake distribution[1]	Score distribution[1]	Spear RC to total MSDPS[2]
Serving/day						
Whole grain	1.40 (0.35-6.81)	1.75 (0.44-8.52)	0.38	0.71 (0.12-4.44)	0.89 (0.15-5.55)	0.09
Fruits	1.81 (0.76-7.33)	4.56 (0.00-9.40)	0.15	3.43 (0.51-16.16)	5.02 (0.00-9.81)	0.08
Vegetables	0.86 (0.30-4.73)	1.44 (0.50-7.90)	0.37	2.25 (0.40-10.21)	3.67 (0.67-10.00)	0.24
Dairy	0.22 (0.03-2.25)	0.11 (0.01-8.70)	0.23	1.45 (0.01-5.94)	0.71 (0.00-9.76)	0.22
Serving/week						
Fish and other sea food	0.00 (0.00-0.21)	0.01 (0.00-0.36)	0.27	0.08 (0.00-1.19)	0.14 (0.00-1.99)	0.21
Poultry	0.62 (0.00-0.83)	1.56 (0.66-2.08)	-0.31	0.20 (0.00-1.46)	0.52 (0.00-3.66)	0.21
Olives, legumes and nuts	4.33 (0.71-61.50)	9.00 (0.00-9.97)	-0.14	10.15 (0.22-115.87)	0.00 (0.00-9.92)	-0.29
Potatoes and other starchy roots	4.07 (0.86-8.09)	5.52 (0.00-9.54)	0.22	0.89 (0.01-11.36)	2.78 (0.00-8.72)	0.18
Eggs	0.65 (0.00.21-0.65)	2.18 (0.72-2.18)	-0.60	0.43 (0.05-3.06)	1.45 (0.16-9.77)	0.00
Sweets	8.34 (0.15-16.06)	0 (0.00-0.52)	-0.54	2.61 (0.10-13.95)	4.62 (0.00-9.78)	0.06
Meat	1.00 (0.28-2.13)	8.26 (2.03-9.94)	-0.00	0.55 (0.02-1.44)	5.54 (0.21-9.96)	0.39
Olive oil	0.00 (0.00-7.12)	0.00 (0.00-5.00)	0.61	1.64 (0.00-14.24)	5.00 (0.00-5.00)	0.11

*Statistically significant between PCa cases and controls (p<0.05). RC: Rank correlation

[1]Data are median (5th, 95th percentile).

[2]Total MSDPS was the sum of 12 components standardized to a 0-100 scale and weighted to the proportion of daily energy intake from Mediterranean diet foods

Table 3: Characteristics of participants across the mediterranean-style dietary pattern score (MSDPD) tertile categories in an Iranian case-control study of prostate cancer in 2011 to 2012[1]

	Cases MSDPS tertiles				Controls MSDPS tertiles			
	1	2	3	P trend[2]	1	2	3	P trend[2]
MSDPS, range[3]	2.07-8.10	8.11-12.20	12.21-28.06		2.5-11.54	11.55-18.44	18.45-54.64	
MSDPS, median	4.80	9.27	18.15		8.41	14.75	20.79	
Age, y	56	58	58	0.40	55	55	53	0.20
BMI, (kg/m^2)	26.8	29.3	27.2	0.80	24.8	24.9	25.5	0.46
University education	31	17	17	0.36	51	48	57	0.62
Current smokers[4], (%)	56	41	41	0.40	3	6	6	0.57
Married, (%)	100	100	100		84	90	97	0.08

BMI: Body mass index, *Statistically significant between case and control groups (p<0.05)

[1]All values are reported as mean or percentages unless otherwise noted. Analyses are adjusted for age.

[2]The p value for trend was determined using the linear regression coefficient MSDPS for continues variables and logistic regression coefficient for dichotomous variables.

[3]Possible point ranges from 0 to 100, median and range.

[4]Smoking status was classified according to World Health Organization guidelines

Table 4: Multivariate adjusted odds ratios for prostate cancer risk across the mediterranean dietary score (MDS) tertile categories in a case-control study of prostate cancer in Iran

	Controls (n)	Cases (n)	Age adjusted OR	95% CI	P-trend	Multivariate adjusted OR*	95% CI	P-trend
MDS								
Tertile 1	32	33	1.00			1.00		
Tertile 2	34	10	0.28	0.12-0.67	<0.001	0.31	0.10-0.92	0.01
Tertile 3	33	7	0.20	0.08-0.53		0.28	0.08-0.91	

*Age, BMI, Smoking, Energy intake, having diabetes and Education level were also included in the regression models as covariates

components that are also representative of a general prudent dietary pattern (Schwingshackl and Hoffmann, 2014). Furthermore, traditionally, the MD is based on both lifestyle (physical activity and tendency to stay in rural settings with less air pollution than in urban ones) and food habit of the European coastal regions of the mid-twentieth century (Marmot *et al*., 2007).

Although it is useful to explore the relative importance of each of the components of the MD (and the possible biological mechanisms involved), it is important to emphasize that no one component was responsible individually for the observed association (Buckland *et al*., 2011). The overall Mediterranean dietary pattern take the advantage that it combines the health effects of many food groups and the biological interactions that take place between them (cumulative effect).

Olive oil is often considered characteristic of the MD, though in Egypt and Malta, olive oil consumption is negligible (Noah and Truswell, 2001). Theprobable role of olive oil on PCa is based on two mechanisms (direct and indirect) (Ferris-Tortajada *et al*., 2012). The direct mechanism is based on its ingredients; It contains oleic acid, low content of saturated lipids, high concentration of vitamin E, squalene and phenolic compounds. The

Table 5: Multivariate adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Prostate cancer (PCa) by components of the mediterranean-style dietary pattern in a case-control study in Iran[1,2]

	-- Multivariate adjusted PCa risk --		
	OR[2]	95% CI	p
Whole grain	1.89	0.74-4.80	0.18
Fruit	0.29	0.11-0.78	0.01
Vegetables	0.03	0.00-0.16	0.00
Dairy	0.08	0.02-0.29	0.00
Fish and other seafood	0.06	0.01-0.26	0.00
Poultry	7.50	0.00	0.99
Olives, legumes and nuts	0.03	0.00-0.19	0.00
Potatoes and other starchy roots	7.30	2.19-24.26	0.00
Eggs	10.69	1.48-77.02	0.01
Sweets	7.65	2.39-24.46	0.00
Meat	3.40	1.20-9.62	0.02
Olive oil	0.40	0.15-1.07	0.07

[1]Values are adjusted for age, total energy intake, BMI, smoking and education level. [2]Reference (≤median)

indirect effect is based on the dietary pattern; increasing intake of salad and vegetables (due to greater palatability) and decreasing intake of animal fat (due to reduced requirement).

The MD is characterized by a regular intake of white fish from small to medium size, caught in fresh water and marine coastal areas. Studies conducted to assess the association between fish consumption and prostate cancer (PCA) risk are inconclusive. In a recent large multiethnic, population-based case-control study (Joshi *et al*., 2012) (1,096 controls, 717 localized and 1,140 advanced PCa cases) high white fish intake was correlated to increased risk of advanced PCa among men who cooked with high-temperature methods (grilling, pan-frying and oven-broiling) until fish was well done (p-trend = 0.001). No associations were detected among men who cooked fish at low temperature.

In another nested case-control study (Torfadottir *et al*., 2013) in Iceland (a country with a tradition of extremely high fish product consumption) high fish consumption in early- and midlife was not associated with overall or advanced prostate cancer. However men consuming fish oil in later life had a 57% lower risk of advanced prostate cancer. In general we can say that there is limited evidence that a high intake of omega-3 decreases the risk of PC (Ferris-Tortajada *et al*., 2012). Unlike the results of our study, some of the studies didn't show a protective effect for fruits or vegetable intake against PCa risk. For example, in a recent meta-analysis by Meng *et al*. (2013), they didn't find a significant protective effect for fruits and vegetable against PCa risk. But according to the researcher statements, most enrolled studies in that meta-analysis, were from developed countries. Whether the non-significant relationship applies to low-income areas with a nutritional deficiency in vegetable and fruit intake is unknown. Studies in developing countries such as Iran, can provide great opportunities to assess the association between diet and chronic diseases (Willet, 1998). As economic resources are severely restricted in developing countries, small economic difference will increase between-person variations in dietary variables (Willett, 2012). Thus link between these dietary variables and disease could be detected easily. Furthermore studies have shown that the role of specific vegetable subgroups (eg, tomato sauce, cruciferous) rather than the total vegetables might be more important (Richman *et al*., 2012; Giovannucci *et al*., 2002). A possible link between adherence to an MD and reduced risk of prostate cancer might be explained by the high consumption of tomatoes (Schwingshackl and Hoffmann, 2014). Experimental data have shown that lycopene (the most relevant functional ingredient in tomato) has an important role in cancer prevention (Schwingshackl and Hoffmann, 2014). Lycopene has antioxidant capacities and furthermore is associated with down regulation mechanisms of the inflammatory response (Wertz *et al*., 2009).

Before the implications of our findings are considered, it is necessary to consider potential limitations. First, like other case-control studies, selection bias and recall bias were inevitable. High response rate (85%) in this study reduced the risk for selective participation based on the lifestyle practices (such as diet). In case-control studies, there is the possibility that cases may recall their diets differently after PCa diagnosis (recall bias). However, our participants had little information about the role of diet and nutrients in the PCa risk, which should have reduced the possibility of recall bias. Furthermore, using hospital controls and administering validated FFQs by trained interviewers in a hospital setting might have further decreased the chance for recall bias and improved the quality of information among cases and controls (D'Avanzo *et al*., 1997). Second, because dietary intake was measured through a self-administered FFQ, information bias was inevitable. This might lead to attenuation of relations (Jessri *et al*., 2011). In the current study, a validated FFQ was applied which provided subjects with the option of answering in terms of day, week or month. In theory, an open-ended frequency response format might maintain further precision in reporting as the frequency of use is truly a continuous rather than a categorical variable (Willett, 2012).

The strengths of our study was registering only incident cases. We asked incident PCa patients diagnosed within 6 month of the interview to recall their diets from 1 year before diagnosis to take into account seasonal variations so that responses should not be dependent on the time of the year and be representative of habitual long-term intake. Furthermore since cases, whose disease diagnosis was less than six months (incident case), were included in this study the chance of diet modification was not high. In a case-control study, exposures are assessed retrospectively (with the

exception of the nested case-control design), often by interview or questionnaire. By using only incident cases, we had a much greater confidence that exposures occurred before the onset of disease.

Conclusion: In conclusion, the present study shows that high adherence to MD might be associated with reduced risk from PCa and is therefore of clinical as well as public health significance. Thus, recommendations to follow this pattern might be beneficial with respect to primary prevention in Iranian men.

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