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ORIGINAL ARTICLE

Adherence to Mediterranean diet and risk of prostate cancer

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ABSTRACT

In Europe, countries following the traditional Mediterranean Diet (MeDi), particularly Southern European countries, have lower prostate cancer (PCa) incidence and mortality compared to other European regions. In the present study, we investigated the association between the MeDi and the relative risk of PCa and tumor aggressiveness in a Spanish population. Among individual score components, it has been found that subjects with PCa were less likely to consume olive oil as the main culinary fat, vegetables, fruits and fish than those without. However, these differences were not statistically significative. A high intake of fruit, vegetables and cooked tomato sauce Mediterranean style (sofrito) was related to less PCa aggressiveness. Results showed that there are no differences in the score of adherence to the Mediterranean dietary patterns between cases and controls, with mean values of 8.37 ± 1.80 and 8.25 ± 2.48, respectively. However, MeDi was associated with lower PCa agressiveness according to Gleason score. Hence, relations between Mediterranean dietary patterns and PCa are still inconclusive and merit further investigations. Further large-scale studies are required to clarify the effect of MeDi on prostate health, in order to establish the role of this diet in the prevention of PCa.

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Introduction

Prostate cancer (PCa) is the second most common cancer in men, with nearly a million new cases diagnosed world-wide per year [1–3]. Diet, lifestyle, environmental and genetic factors are hypothesized to play a role in these differences [2]. In Europe, countries following the traditional Mediterranean Diet (MeDi), particularly Southern European countries, have lower PCa incidence and mortality compared to other European regions [4]. The general features of this diet are high intake of vegetables, fruits, nuts, legumes, cereals and lean fish, moderate consumption of alcohol and low amounts of milk and read meat. Several of these individual food items, or the nutrients they contain, have been associated with a reduced risk of prostate cancer [5]. Trichopoulou et al. [6] calculated that 10% of the incidence of PCa could be prevented if the populations of highly developed Western countries could shift to the traditional healthy MeDi.

There are a few studies that have assessed the effect of the MeDi on cancer prostate incidence in non-Mediterranean population. The European Prospective Investigation into Cancer and Nutrition (EPIC) study showed that a MeDi is particularly beneficial in protecting against PCa [7]. Schwingshackl and Hoffmann [8] in a recent meta-analysis showed that high adherence to a MeDi is associated with a significant 4% reduction in the risk of PC. Kenfield et al. [9] described that adherence to a MeDi evaluated through a MeDi Score was not associated with risk of advanced PCa or disease progression in a prospective study following 47,867 US men. However, greater adherence to the MeDi after diagnosis of nonmetastatatic cancer was associated with lower overall mortality. Bosire et al. [10] report no relationship between the alternate Mediterranean diet score diet and the risk of PCa in the National Institutes of Health (NIH)-AARP Diet and Health Study cohort (293,464 US men). In addition, it was found little support for an association between

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the MeDi and PCa in two Northern European case-control study [5,11]. In a recent study, Erdrich et al. [12] carried out a small pilot study in which 20 men with diagnosed PCa adhered to a MeDi. A significant reduction in DNA damage compared to baseline was apparent, with particular benefit noted for overall adherence to the diet ($p = .013$), ostensibly due to reduction in reactive oxidant species. There is only one study carried out in Mediterranean population that explores the association of the Mediterranean dietary pattern with PCa risk. Castelló et al. [13] showed that a Mediterranean dietary pattern is associated to lower risk of aggressive PCa in a Spanish population. This association was not observed with Prudent pattern, which combines vegetables and fruits with low-fat dairy products, whole grains and juices [13]. Due to the contradiction between the studies, the impact of MeDi adherence on prostate health remains unclear.

In the present study, we investigated the association between the MeDi and the relative risk of PCa and tumor aggressiveness in a Spanish population. To the best of our knowledge, this is the first study specifically investigating PCa risk and the MeDi using a score in Spain.

Materials and methods

Patients and data collection

Patient recruitment was carried out in the Department of Urology, University Hospital "Virgen de las Nieves", Granada. Research protocols were approved by the Institutional Review Boards at the Hospital. All men enrolled in the study were patients with PSA levels above 4 ng/ml with a suspicion of developing PCa and upon whom a biopsy was performed. After the analysis of the Anatomy Pathology, subjects were classified in patients ($n = 254$) and controls ($n = 302$). Informed consents were required from all participants in the trial, and the study has been approved by local institutional review boards and Ethics Committees and conducted in accordance with the Declaration of Helsinki.

Consented patients were interviewed by the urologists and were asked to respond to a series of structured questionnaires that solicited information, which included background characteristics, occupation, family history of PCa, comorbid conditions, PCa diagnosis and physical activity level. At the time of interview subjects, height was measured using a stadiometer and weight was measured using a floor scale. BMI was then calculated using the formula weight (Kg)/height $(m)^2$.

Clinical parameters

PCa characteristics, which included Gleason grade and serum PSA level, were obtained by the urologists. PCa aggressiveness was classified as a function of Gleason grading system. The Gleason score grades the severity of prostate tumors according to tumor histology. PCa with a total Gleason score ≥ 7 was considered histologically aggressive; while those graded <7 were regarded nonaggressive [14].

Nutritional survey

The Mediterranean Diet Score (MDS), a validated MeDi questionnaire [15] was completed in a face-to-face interview with participants by specifically trained dieticians. The questionnaire assessed the consumption of elements included in the MeDi (olive oil, wine, fruits, vegetables, fish, legumes and whole-grain intake). A low consumption of meat or meat products, butter, margarine or cream, carbonated beverages and commercial sweet or pastries were also included in the composite score questionnaire [15].

Statistical methods

SPSS v.20.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Chi-square and Fisher's test was used to evaluate the differences in distribution of categorical variables. Shapiro–Wilk's test was performed to check the normality of the variables.

The analysis of the relation of MeDi and PCa risk and aggressiveness was performed by means of binary logistic regression analysis. Potential confunders were included, like age and family history of PCa. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated.

Results and discussion

The study population is described in Table 1. The cases were somewhat older than the controls and were more likely to be employed in agricultural work and to have a family history of PCa. Nutritional status revealed that 52.3% of cases were overweight and 27.9% were obese versus only 19.8% patients with an adequate BMI. There were no major differences between cases and controls concerning BMI, smoking status, physical activity and coffee intake.

Exposure to inadequate diets through life may influence PCa progression due to the long pre-clinical stage [16]. Schwingshackl and Hoffmann in a meta-analysis [8] have confirmed the concept that a high

Table 1. Sociodemographic characteristics of case and control participants.

	Biopsy − (%)	Biopsy + (%)	p^*
Age			
≤65	42.5	24.5	.005
[66–75]	36.2	46.3	
>75	21.3	29.2	
Diabetes			
With diabetes	26.5	16.3	.125
Without diabetes	73.5	83.7	
Alcohol			
Yes	14.2	10.5	.515
No	85.8	89.5	
Familiar cancer			
None	62.6	39.8	.005
Prostate cancer	8.3	12.5	
Others	29.1	47.7	
BMI			
Normal	20.5	19.8	.468
Overweight	45.2	52.3	
Obesity	34.3	27.9	
Smoking			
Smoker	21.5	23.6	.125
Ex-smoker	45.3	39.5	
Non smoker	33.2	36.9	
Physical activity			
No	59.2	58.3	.122
Yes	40.8	41.7	
Coffee			
Without coffee	63.2	59.6	.598
With coffee	36.8	40.4	
Job (%)			
Agriculture	22.4	25.3	.005
Industry	13.2	16.6	
Construction	12.7	7.2	
Others	51.7	50.9	

*Chi-square or Fisher's test p values.

adherence to the MeDi was associated with a significant reduction in both mortality and cancer incidence by 10% (RR: 0.90, 95% CI 0.86–0.95, $p < .0001$). In particular, the authors assessed that the risk of PCa could be reduced by 4% with a high adherence to MeDi. In their review, the authors confirmed both the concept that dietary factors could reduce cancer risk through several mechanisms, involving the suppression of spontaneous mutations of DNA, the modulation of cell proliferation, or the methylation of DNA and the induction of apoptosis. Schwingshackl and Hoffmann also reiterated the highly protective role of the olive oil, which is one of the main components of the MeDi.

In this study, the percentage of achievement of the specific MeDi items was compared according to the biopsy results (Table 2). It has been found that subjects with PCa were less likely to consume olive oil as the main culinary fat (98.5% vs. 100%), vegetables (48.57% vs. 50.66%), fruits (58.57% vs. 61.33%) and fish (49.32% vs. 50.30%) than those without. On the contrary, cases consume more quantity of meat product, butter and carbonated beverages. However, these differences were not statistically significative.

Olive oil is the major common characteristic of diet in Mediterranean populations, where it accounts for one to two-thirds of total vegetable fat intake and is therefore a relevant source not only of unsaturated fats, but of several other dietary components and micronutrients, as well. An Australian case-control study compared subjects consuming <0.25 and ≥0.25 l/month to nonusers of olive oil, and reported no significant association between olive oil consumption and PCa risk (both ORs =0.8) [17]. In a population-based case–control study was conducted in New Zealand increasing levels of MUFA-rich vegetable oil intake were associated with a progressive reduction in PCa risk [Relative risk (RR) = 0.5; 95% CI: 0.3–0.9; > 5.5 ml per day vs. nonconsumption, $p = .005$] [18]. However, PCa risk was not associated with intake of total MUFA or its major animal food sources. Fruits and vegetables contain numerous components known to have favorable effects on inflammatory, cellular redox, as well as metabolic processes and endothelial function, which might add up to their tumor-protective impact. In addition, regular consumption of fruits and vegetables facilitates weight management in overweight subjects to counter obesity as a risk factor for cancer [19]. The obesity has been related with the oxidative stress and the mitochondrial dysfunction. In fact, mitochondrial DNA mutations have been found to play a role in the genesis of numerous cancers [20] A meta-analysis from 12 case–control studies (5777 cases and 9805 control) and from 12 cohort studies (445,820 subjects), concerning fish intake and the incidence and mortality of PCa [1,21], did not observe any significant association between fish consumption and a reduction of PCa incidence among cohort studies (RR: 1.01; 95% CI: 0.90–1.14; $p = .83$). Authors observed a weak association between fish intake and reduction of PCa incidence from case–control studies (RR: 0.85; 95% CI: 0.72–1.00; $p = .05$) (Table 3).

One of the potential reasons for inconsistent results of epidemiological studies examining the association between MeDi and PCa may be that most of the studies had a small number of advanced tumors [22]. Potential associations between different components of the MeDi and prostate tumor aggressiveness (Gleason score ≥7) were explored. Among individual score components, a high intake of fruit, vegetables and cooked tomato sauce Mediterranean style (sofrito) is related to less aggressiveness. However, there are controversial points of the effect of MeDi focuses on testosterone therapy in Pca men [23]. MeDi could contribute to elevate testosterone levels and the testosterone replacement therapy has a protective role against high-grade PCa [24,25] with no difference in overall mortality and incidence of PCa progression, in both, intermittent hormone therapy and continuous

Table 2. Individual components of Mediterranean diet score and prostate cancer risk.

Items		Biopsy − (%)	Biopsy + (%)	*F*	*p*
Do you use olive oil as main culinary fat?	Yes	100	98.5	0.146	.732
How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥4 tbsp	62.6	65.71	0.146	.732
How many vegetable servings do you consume per day? (1 serving: 200 g [consider side dishes as half a serving])	≥2 (≥1 portion raw or as a salad)	50.66	48.57	0.064	.869
How many fruit units (including natural fruit juices) do you consume per day?	≥3	61.33	58.57	0.115	.738
How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	<1	68.0	72.85	0.409	.587
How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	<1	81.33	85.71	0.503	.478
How many sweet or carbonated beverages do you drink per day?	<1	68.0	78.57	2.058	.151
How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥3	50.30	49.32	0.064	.869
How many servings of pulses do you consume per week? (1 serving: 150 g)	≥3	38.66	38.57	0.001	.563
How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	<3	58.66	62.85	0.266	.615
How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g)	≥3	39.00	40.00	1.007	.203
Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes	65.33	67.14	0.053	.862
How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with *sofrito* (sauce with tomato and onion, leek or garlic simmered in olive oil)?	≥2	81.66	81.42	0.963	.423
How many glasses of wine do you consume per week?	≥7	47.66	48.57	2.886	.395

F: Fisher statistic.

Table 3. Individual components of Mediterranean diet score and prostate cancer aggressiveness.

Items		Gleason <7	Gleason ≥7	*F*	*p*
Do you use olive oil as main culinary fat?	Yes	98.48	100	0.138	1.00
How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥4 tbsp	63.63	65.55	0.221	.720
How many vegetable servings do you consume per day? (1 serving: 200 g [consider side dishes as half a serving])	≥2 (≥1 portion raw or as a salad)	66.96	54.34	6.592	.031
How many fruit units (including natural fruit juices) do you consume per day?	≥3	57.57	44.44	6.981	.023
How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	<1	44.24	46.44	3.393	.113
How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	<1	83.33	85.24	1.758	.340
How many sweet or carbonated beverages do you drink per day?	<1	77.27	77.77	0.001	1.00
How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥3	46.96	44.44	0.020	1.00
How many servings of pulses do you consume per week? (1 serving: 150 g)	≥3	40.90	11.11	3.006	.141
How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits or custard?	<3	70.60	77.77	0.998	.470
How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g)	≥3	37.87	33.33	0.07	1.00
Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger or sausage?	Yes	82.12	88.88	2.506	.150
How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with *sofrito* (sauce with tomato and onion, leek or garlic simmered in olive oil)?	≥2	83.33	44.44	7.137	.018
How many glasses of wine do you consume per week?	≥7	48.48	43.33	0.731	.489

F: Fisher statistic.

hormone therapy [26]. These observations are in agreement with the fact that PCa men, who are receive androgen deprivation treatment, are classified at risk of developing insulin resistance and hyperglycemia, which leads them to an increased risk of cardiovascular diseases [27].

Mediterranean sofrito is a key component of the MeDi, provides nutritional interest due to its high content in bioactive compounds from garlic and onion such as isoflavone, tomato such as lycopene and olive oil, and especially to the lipid matrix in which these compounds are found [28,29]. Studies have shown

that plasma steroid hormones have been implicated in the development of the benign prostatic hyperplasia and PCa [30]. The genistein, a soy phytoestrogen, is involved in the estrogen and androgen signaling pathways and may protect against PCa [31]. Lycopene is the pigment principally responsible for the characteristic deep-red color of tomato products. Peisch et al. [32] suggested that several dietary factors, such as tomato sauce/lycopene and vegetables may have a role in reducing risk of PCa progression. Recently, it has been found that the presence of other ingredients in Mediterranean sofrito such as extra virgin olive oil, onion and garlic improve the bioavailability of lycopene [33]. In addition, it was observed that the plasma concentration of lycopene significantly increased after the consumption of tomatoes meal cooked in olive oil, compared to the consumption of tomatoes meals cooked without olive oil [34]. Some studies have hypothesized that the consumption of a diet rich in lycopene-containing foods reduces the aggressive potential of PCa by inhibiting the neoangiogenesis that occurs in tumor development [35]. The main role of lycopene seems to be related to producing a modulation in redox activity, enzyme detoxification, inhibition of cell proliferation and apoptosis induction [36]. Recent studies have proved that lycopene increased the amount of some protective enzymes, such as glutathione-S-transferase-omega-1, peroxiredoxin-1 and sulfide-quinone oxidoreductase. Proteins, such as ERO1-like protein-α or CLIC-1, usually involved in reactive oxygen species generation, have been shown to be downregulated after treatment with lycopene. This indicates a potential for lycopene to lower the risk for the generation of reactive oxygen species and to reduce oxidative stress [37]. Most case–control studies have demonstrated a significant, inverse association between intakes of vegetables and the risk of advanced prostate cancer, with risk estimates (ORs) ranged from 0.36 to 0.96 [38,39]. However, no association was found between intake of vegetables and the risk of advanced prostate cancer in most cohort studies [40,41]. Similarly, fruit intake was overall not associated with the risk of advanced prostate cancer in both case–control [38,42] and cohort studies [41].

Table 4 showed that there are no differences in the score of adherence to the Mediterranean dietary patterns between cases and controls, with mean values of 8.37 ± 1.80 and 8.25 ± 2.48, respectively. These results are in agreement with previous studies that found no significant association between MeDi pattern and PCa risk [5,9–11,13]. These results might be affected by the blunt scoring method, which is insufficient to consider all dietary factors, or by counter-balancing the protective or promoting effect of each component when combined together [3]. It should be taken into account that is difficult to compare the studies accurately, and the possibility of a controversial outcome is higher. The differences between studies include the following: diverse versions or modifications of indices; various index components; scoring methods and categorization criteria [3]. Finally, most of the studies were conducted in North Europe and North America, indicating that the populations involved in the studies are relatively similar. Therefore, further studies should be conducted actively in Mediterranean population from different countries.

Table 4. Mediterranean diet score and PC risk and aggressiveness.

	Mean[a]	SD	Hazard ratio	95.0% C.I.	*p* value
Biopsy					
Positive	8.37	1.805	0.976	0.875–1.003	.314
Negative	8.25	2.482			
Gleason					
Gleason ≥7	7.25	1.062	1.008	0.997–1.023	.050
<7	9.50	1.092			

[a]Scores on the index scale range from 1 to 14; Age (continuous) and family history of prostate cancer were included in the regression models as covariates; C.I.: confidence interval.

There is an inverse association between MDS and risk of aggressive tumors according to Gleason score (Table 4). These results are in agreement with several studies in which a protective effect of dietary patterns with high consumption of fruits and vegetables, fish and olive oil for aggressive tumors has been described [13,43–45]. In addition, with those diagnosed with nonmetastatic PCa at baseline, adherence to the MeDi was associated with lower overall mortality, suggesting possible beneficial effects [9]. In contrast, Mehdad and coworkers [16] found no association between diet and tumor aggressiveness (Gleason score $>=7$).

In conclusion, there are few studies that have assessed the effect of the MeDi on cancer prostate incidence, specially in Mediterranean population. Recent data do not support associations to adherence to a MeDi and risk of PCa. However, Mediterranean eating pattern was associated with lower PCa agressiveness. Hence, relations between Mediterranean dietary patterns and PCa are still inconclusive and merit further investigations. Further large-scale studies are required to clarify the effect of MeDi on prostate health, in order to establish the role of this diet in the prevention of PCa.

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