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ORIGINAL ARTICLE

The influence of nutritional factors on prostate cancer incidence and aggressiveness

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ABSTRACT

There is an increasing evidence for a link between nutrition, lifestyle and prostate cancer (PCa) development and/or progression of disease. The objective of this study was to examine the association between dietary factors and PCa incidence and aggressiveness in a case-control study. After the analysis of the anatomic pathology, subjects were classified in patients with PCa ($n = 157$) and controls ($n = 158$). Clinical data including Gleason score, PSA values and biopsy results, were compiled. Frequencies of food consumption and sociodemographic data were also obtained. The results showed that physical activity was significantly higher in control ($p < .022$). It was also found that some nutritional habits offer a protective effect among studied subjects, like high nuts ($p = .041$) and fish ($p = .041$) intakes. Moreover, there was a significant reduction in risk ($p = .029$) in cases with a higher fruits and vegetables intakes. A decreased risk of aggressive PCa was associated with fruits, vegetables, legumes and fish intakes. However, these relationships were not statistically significant when data were adjusted for covariates. In conclusion, this study found an inverse association between PCa risk and the intake of fruits and vegetables, fish and nuts. The results suggested that a diet with higher intakes of these foods as Mediterranean diet may lower the risk of PCa in the studied population. As dietary factors are modifiable, identifying food groups or dietary patterns that modulate the risk of PCa and its aggressiveness can offer effective and practical strategies for its primary prevention.

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1. Introduction

The available information in recent years shows that among various neoplasms, prostate cancer (PCa) has the highest estimated new cases in men [1]. Because of the growing incidence of PCa and the low death rates, prevention of PCa and specifically aggressiveness and treatment resistances in PCa is an important issue [2]. There is an increasing evidence for a link between nutrition, lifestyle and PCa development [3,4]. It has been showed that lifestyle modifications such as smoking cessation, exercise and weight control offer opportunities to reduce the risk of developing PCa [5]. Consequently, a large body of literature endeavors to elucidate the role of lifestyle factors, including diet, in PCa risk, development of the tumor and successful survivorship. In addition, the large disparity in PCa incidence between the Eastern and the Western hemispheres, points to a key role of environmental factors, such as diet, as an etiologic factor in this disease [6].

Different studies provide data about PCa and its strong associations with metabolic, hormonal and inflammatory profile. In PCa it is clear that obesity and metabolic syndrome are important risk factors [3,4]. It has been suggested that a higher body mass index (BMI), is positively associated with an increased risk of developing an aggressive form of prostate cancer and consequently an increase in its mortality rate. Besides, it has been proposed that obesity increases the risk of biochemical recurrence after primary treatment [7]. Insulin resistance, usually related to overweight/obesity, are also associated with high PCa risk, although different factors could be responsible for this correlation.

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Contradictory results have also been found concerning the relationship of benign prostatic hyperplasia, with total caloric or fat intake, BMI and diabetes [8]. In addition, obesity has also been shown to increase prevalence of other illnesses such as lower urinary tract symptoms, overactive bladder, erectile dysfunction and hypogonadism [9–12].

In other cancer like breast cancer, the consumption of fruits and vegetables, dietary fiber intake, vitamin supplementation along with the intake of probiotic products, are the most extensively studied by a negative association to cancer risk [13]. In PCa it is clear that obesity and metabolic syndrome are important risk factors [3,4]. Based on the epidemiological studies, several dietary factors and vitamins/supplements may be associated with PCa risk and/or progression of disease [14]. Many nutrients show potential benefits in helping to slow progression and reduce recurrence, as well as complementing conventional treatment to improve quality of life [15]. Nutraceuticals and supplements, particularly antioxidants, polyphenols and soy have evidence for benefit for prevention of PCa and progression of the disease [3]. Comhaire and Mahmoud [16] suggest food supplementation with the liposterolic extract of Serenoa repens and a combination of the antioxidants selenium, lycopene and natural vitamin E, together with fish oil to prevent or delay PCa and benign prostatis hypertrophy. Trends in the published data suggest that consumption of carbohydrates, saturated, trans and ω-6 fats and certain vitamin supplements may promote PCa risk and progression [17] . Conversely, consumption of fruit, vegetables, dietary fiber and ω-3 fatty acids seem to slow the risk and progression of the disease [18], even to produce a small reduction in prostate cancer risk [19].

The high prevalence of "latent" PCa compared with clinically significant disease suggests that dietary factors influencing the later stages of PCa progression may be relevant to effective intervention. Epidemiological studies suggest that diet is a key factor in the etiology of aggressive PCa [20]. Moreover, the WHO) reported that approximately a 30% of cancer deaths are due to five behavioural risk factors and diet, such as high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco and alcohol habits [13]. For some slow growing cancers, such as PCa, presentation with a more aggressive form at diagnosis confers risk of a worse outcome than those diagnoses with less aggressive disease. There is a need to identify adjustable behaviours such as diet and exercise that may decrease not only the overall risk of cancer, but also the risk of aggressive disease within specific types of cancer [21]. Because of the limited number of studies available for a secondary outcome assessment, additional studies of aggressive and fatal disease are eagerly awaited [22].

Despite the information available, a common consensus on which nutrients or food groups may be beneficial and which could be harmful in PCa is lacking [15]. Recently, a dietary pattern that includes rich fruits and vegetables, reduced refined carbohydrates, total and saturated fats and reduced cooked meats has been related to PCa risk reduction [14]. Recent publications included that significant linear trend between the Western pattern, the carbohydrate pattern and the increment of PCa risk, moreover there are evidence suggesting that high adherence to a Mediterranean diet is associated with reduced risk of overall cancer mortality as well as a reduced risk of incidence of several cancer types including PCa [23,24]. Therefore more research is needed to elucidate the effects of consumption of particular food and how this relates to PCa. The objective of this study was to examine the association between dietary factors and PCa incidence and aggressiveness in a case-control study.

2. Materials and methods

2.1 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 anatomic pathology, subjects were classified in patients ($n = 157$) and controls ($n = 158$). All research subjects provided written informed consent. Some of the samples were not well classified at the biopsy examination and hence were lost in consequent analysis.

Consented patients were interviewed by the urologists and were asked to respond to a series of structured questionnaires that solicited information, which included back-ground characteristics, occupation and family history of PCa, comorbid conditions, PCa diagnosis and physical activity level. In addition, patients were interviewed using a food frequency structured questionnaire by trained dieticians. Food consumption was recorded according to whether an item had been consumed or not during the last year, the number of times it was consumed per week and the amount

Table 1. Sociodemographic characteristics of case and control participants.

	Biopsy − (%)	Biopsy + (%)	All (%)	p^a	Gleason <7 (%)	Gleason ≥7 (%)	p^a
Diabetes							
With diabetes	26.2	16.5	21.4	.125	26.4	26.0	.570
Without diabetes	73.8	83.5	78.6		73.6	74.0	
Alcohol							
Yes	13.9	10.0	11.9	.515	17.0	10.4	.398
No	86.1	90.0	88.1		83.0	89.6	
Familiar cancer							
None	63.8	43.7	53.8	.005	68.4	58.3	.364
Prostate cancer	9.5	7.8	8.7		10.5	8.3	
Others	26.7	48.5	37.5		21.1	33.3	
Body mass index							
Normal	20.2	19.3	19.7	.468	20.3	20.0	.999
Overweight	44.0	51.8	48.0		44.1	44.0	
Obesity	35.8	28.9	32.3		35.6	36.0	
Smoking							
Smoker	20.9	23.4	22.2	.125	18.6	23.5	.590
Ex-smoker	46.4	39.6	43.0		50.8	41.2	
Non smoker	32.7	36.9	34.8		30.5	35.3	
Physical activity							
No	59.6	43.6	51.6	.022	61.0	58.0	.450
Yes	40.4	56.4	48.4		39.0	42.0	
Coffee							
Without coffee	63.8	58.2	61.0	.598	64.7	62.9	.536
With coffee	36.2	41.8	39.0		35.3	37.1	
Age							
≤65	26.3	43.3	34.8	.007	30.8	21.8	.125
66–75	46.2	36.3	41.2		48.7	43.6	
>75	27.6	20.4	24.0		20.5	34.6	
Flavones intake							
Yes	7.2	11.6	9.5	.433	11.6	2.5	.118
No	92.8	88.4	90.5		88.4	97.5	

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

consumed each time (in household measures). 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 $(m)^2$.

2.2 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 tumours according to tumour histology. PCa with a total Gleason score ≥7 was considered histologically aggressive; while those graded <7 were regarded nonaggressive [25]. BMI was calculated from weight and height measurements obtained according to the standard calculation of weight (Kg) divided by height (m^2).

2.3 Statistical methods

SPSS v.20.0 (SPSS Inc., Chicago, IL) [26] was used for statistical analysis. Chi-square and Fisher's test was used to evaluate the differences in distribution of categorical variables, and Mann-Whitney test or Students *t*-test analysis, was used to check the differences in distribution of continuous variables. Shapiro-Wilk's test was performed to check the normality of the variables. Nutrients and food consumption variables were distributed in the approximated marginal tertiles.

Odds ratios (OR) for risk of PCa and for the Gleason index value, associated with nutrients and foods and the corresponding 95% confidence intervals (CI) for a tertile increment of intake of the respective food groups, were estimated using unconditional logistic regression model. For the risk on PCa the regression was performed with and without adjustment of four covariates: age (categorized in 3-year groups), alcohol (no/yes), diabetes (no/yes) and physical activity (no/yes). In the case of the Gleason index value, the covariates selected were: age (categorized in 3-year groups), familiar Cancer (no/yes) and smoking (smoker, ex-smoker and non-smoker).

To select the most appropriate covariates for each regression, a multiple backward stepwise logistic regression was computed. Tests for trend associated the increased of intake were performed with the test of Cochran-Armitage. For all the statistical tests, the significance level was set at 0.05.

Table 2. Food consumption of case and control participants.

Variables	Mean	Median	P25	P75	Maximum	SD	p^a
Fruits (g/day)							
Biopsy +	336.6	350.0	175.0	500.0	1250.0	265.83	.178
Biopsy −	387.0	350.0	175.0	525.0	1625.0	270.4	
All	362.2	350.0	175.0	525.0	1625.0	268.5	
Vegetables (g/day)							
Biopsy +	97.5	64.2	42.8	150.0	450.0	78.7	.981
Biopsy −	95.6	64.2	42.8	150.0	321.4	67.2	
All	96.5	64.2	42.8	150.0	450.0	72.8	
Fruits and vegetables (g/day)							
Biopsy +	439.3	414.2	200.0	626.7	1.400	300.7	.329
Biopsy −	479.6	414.2	235.7	650.0	1839.2	297.3	
All	459.8	414.2	217.8	650.0	1839.2	298.7	
Meat (g/day)							
Biopsy +	44.7	42.8	21.4	64.2	150.0	34.2	.203
Biopsy −	52.4	42.8	21.4	64.2	150.0	40.8	
All							
Fish (g/day)							
Biopsy +	51.3	47.4	41.5	47.4	166.0	28.9	.144
Biopsy −	58.5	47.4	47.2	71.1	166.0	33.1	
All	55.0	47.4	47.4	71.1	166.0	31.3	
Cereals (g/day)							
Biopsy +	53.3	52.5	52.5	52.5	157.5	30.2	.398
Biopsy −	57.9	52.5	52.5	52.5	187.5	38.0	
All	55.7	52.5	52.5	52.5	187.5	34.4	
Legumes (g/day)							
Biopsy +	30.7	22.8	22.8	34.2	80.0	18.4	.157
Biopsy −	26.8	22.8	22.8	34.2	80.0	16.4	
All	28.7	22.8	22.8	34.2	80.0	17.4	
Dairy (g/day)							
Biopsy +	290.6	250.0	125	350	500	150.5	.215
Biopsy −	280.3	250.0	125	350	500	190.5	
All	285.4	250.0	125	350	500	175.5	
All	1.2	0	0	0	62.8	8.0	
Eggs (g/day)							
Biopsy +	20.0	17.1	8.5	25.7	102.8	15.1	.445
Biopsy −	19.7	17.1	8.5	25.7	120.0	14.1	
All	19.8	17.1	8.5	25.7	120.0	14.5	
Nuts (g/day)							
Biopsy +	3.8	0	0	2.8	22.8	6.9	.905
Biopsy −	4.6	2.8	0	6.4	20.0	6.3	
All	4.2	0	0	5.7	22.8	6.6	

P25: percentile 25; P75: percentile 75; SD: standard deviation.
[a]Mann-Whitney or t-Student p values.

3. Results and discussion

3.1 Patient characteristics

Physical activity was found to be a lifestyle factor significantly higher in control subjects ($p < .022$) (Table 1). Recently, Morote et al. showed that a sedentary lifestyle is associated with increased risk of PCa detection [27]. The influence of physical activity on the risk of PCa has been analysed in several studies with contradictory results [4,28,29]. However, a meta-analysis including 88,294 men suggests a slight association between physical activity and PCa risk [30]. Body mass index (BMI) mean value in PCa patients (28.1 ± 4.1) was not statistically significant comparing with controls (28.4 ± 4.3). Epidemiological studies on the relationship between obesity and PCa are somewhat conflicting: a Italian cohort study showed a positive association between high BMI and PCa incidence [31], yet the Swedish Cohort study conducted in 15,326 men over 3.5 years of follow up, found no overall association [32]. Obesity may contribute to hormonal changes through the decrease of sex hormone-binding globuline levels and concomitant increase of bioavailable androgens and also by enhancing peripheral aromatization of androgens to estrogens. There are evidence that estrogens either alone or together with androgens, can induce aberrant prostatic growth and subsequent neoplastic transformation. In addition, adipose tissue produces different adipocytokines, like adiponectin, which has been evaluated in different stages of PCa, through contradictory results have also been published [33,34]. Whether the increase of adipocytokines and other inflammatory markers are related only to obesity or to PCa as well needs to be investigated [8]. Smoking habits, alcohol and coffee consumption were similar in the two groups of the present study (Details in Table 1).

Table 3. Food consumption of case participants.

Variables	Mean	Median	P25	P75	Minimum	Maximum	SD	p^a
Fruits (g/day)								
Gleason <7	389.7	350.0	175.0	525.0	0	1250.0	285.6	.049
Gleason ≥7	278.1	175.0	125.0	350.0	0	875.0	231.8	
Vegetables (g/day)								
Gleason <7	90.4	64.2	42.8	150.0	0	428.5	73.6	.309
Gleason ≥7	104.9	64.2	64.2	150.0	0	450.0	83.9	
Fruits and vegetables								
Gleason <7	51.3	487.3	417.8	207.1	708.9	21.4	1400	.192
Gleason ≥7	388.9	325.0	200	500	0	1175.0	256.6	
Meat (g/day)								
Gleason <7	47.5	42.8	21.4	64.2	0	150.0	34.3	.252
Gleason ≥7	41.6	42.8	21.4	53.5	0	150.0	34.2	
Fish (g/day)								
Gleason <7	53.7	47.4	47.4	59.2	23.7	166.0	30.0	.452
Gleason ≥7	48.7	47.4	23.7	47.4	0	166.0	27.91	
Cereals (g/day)								
Gleason <7	48.1	52.5	41.2	52.5	7.5	105.0	18.2	.223
	59.1	52.5	52.5	52.5	7.5	157.5	39.0	
Legumes (g/day)								
Gleason <7	34.0	22.8	22.8	45.7	11.4	80.0	20.8	.190
Gleason ≥7	27.1	22.8	22.8	34.2	11.4	80.0	14.8	
Dairy (g/day)								
Gleason <7	292.1	250.0	125.0	350.0	0	500.0	130.2	.230
Gleason ≥7	288.0	250.0	125.0	350.0	0	500.0	128.5	
Eggs (g/day)								
Gleason <7	18.3	17.1	8.5	17.1	0	51.4	11.1	.590
Gleason ≥7	21.7	17.1	8.5	25.7	0	102.8	18.5	
Nuts (g/day)								
Gleason <7	4.2	0	0	2.8	0	20.0	7.3	.800
Gleason ≥7	3.4	0	0	5.0	0	22.8	6.5	

P25: percentile 25; P75: percentile 75; SD: standard deviation.
[a]Fisher's test *p* values.

A significant association between age and the risk of aggressive PCa was found with a mean value of 67.7 in patients with Gleason score <7 and a mean value of 71.6 in patients with a Gleason score ≥7 (Table 1). Adiposity measurement including BMI and waist circumference have been reported to be positively associated with aggressive prostate cancer [35]. In this study, there were no differences in the BMI between high grade and low grade PCa patients (mean values of 28.7 ± 4.4 and 28.3 ± 4.2, respectively). Other authors have reported that aggressive cases were greater among men older at diagnosis and with greater BMI than their counterparts [27,36]. Recent studies reported that BMI is related to chemotherapy results such as an analysis developed in a Japanese PCa that classified for adverse pathological findings and biochemical recurrence after radical prostatectomy and others reported that BMI <25 kg/m^2 are associated with reduced survival in patients with castrate resistant PCa being treated with docetaxel chemotherapy [37,38]. Tumour aggressiveness was not clearly associated with any of the other studied characteristic.

3.2 Food consumption

Food consumptions reported as total consumption per day in cases and control patients is shown in Table 2. In order to analyse the relation between food consumption and PCa, univariate analyses were conducted. There were not statistically significant differences in food consumption between cases and controls. Table 3 shows intakes of food groups in low and high grade PCa patients. A significant association between fruit consumption and PCa aggressiveness was observed. The fruit intake mean value (g/day) in patients with Gleason score <7 was higher (389.7 ± 285.6) than the intake in cases with a Gleason score ≥7 (mean value 278.1 ± 231.8). There were not differences in intakes between the two studied groups in the other food groups.

Table 4 gives the results of unconditional logistic regression model with and without adjustment of four covariates to study the association of food consumption with PCa risk. In individual unadjusted analyses a significant 18.6% reduction in risk was found between the highest and the lowest fruit intake categories. When data were adjusted for covariates, there was a not statistically significant 20% decrease risk for the highest intake categories. The effect of total consumption of fruit and vegetables on PCa risk was examined. There was a linear trend, with 25% reduction in risk in the highest intake category. In models adjusted for covariates, there was a significant reduction in risk ($p = .029$), with a 22.5% decreased risk in the highest fruit and vegetables intake category. Fruits and vegetables are rich in fibre, micronutrients and

Table 4. Odds ratios of prostate cancer incidence associated with food intake.

	Unadjusted			Adjusted for covariates[a]			
	OR	95% CI Lower limit	95% CI Upper limit	OR	95% CI Lower limit	95% CI Upper limit	*p* value for trend
Fruits (g/day)							
<175	1.000	(Referent)		1.000 (Referent)			
175–350	0.905	0.583	1.040	0.739	0.376	1.454	
>350	0.814	0.484	1.363	0.796	0.373	1.698	
							.178
Vegetables (g/day)							
< 64.28	1.000	(Referent)		1.000 (Referent)			
64.28–150	1.128	0.761	1.670	1.402	0.763	2.578	
>150	0.375	0.099	1.414	0.300	0.053	1.708	
							.888
Total fruits and vegetables (g/day)							
< 297.46	1.000	(Referent)		1.000 (Referent)			
297.46–500	1.077	0.631	1.837	1.012	0.484	2.115	
>500	0.742	0.433	1.272	0.775	0.365	1.645	
							.029
Meat (g/day)							
< 21.42	1.000	(Referent)		1.000 (Referent)			
21.42–64.28	1.023	0.672	1.558	0.906	0.439	1.871	
>64.28	0.647	0.303	1.381	0.707	0.238	2.100	
							.140
Legumes(g/day)							
< 22.85	1.000	(Referent)		1.000 (Referent)			
22.85–34.28	0.816	0.508	1.311	0.740	0.359	1.525	
>34.28	1.185	0.710	1.978	1.063	0.526	2.148	
							.347
Dairy (g/day)							
< 50.0	1.000	(Referent)		1.000 (Referent)			
50.0–125.0	0.915	0.624	1.435	0.890	0.342	1.328	
>125.0	1.123	0.725	1.345	1.034	0.431	1.763	
							.435
Fish(g/day)							
< 25	1.000	(Referent)		1.000 (Referent)			
25–50	1.105	0.713	1.714	1.019	0.526	1.975	
>50	0.567	0.313	1.027	0.418	0.170	1.027	
							.043
Cereals (g/day)							
<30	1.000	(Referent)		1.000 (Referent)			
30–55	0.983	0.684	1.412	0.823	0.433	1.564	
>55	0.667	0.273	1.631	0.547	0.185	1.612	
							.439
Eggs (g/day)							
<17	1.000	(Referent)		1.000 (Referent)			
17–35	0.810	0.552	1.190	0.765	0.421	1.391	
>35	2.667	0.707	1.052	2.305	0.550	9.671	
							.673
Nuts (g/day)							
0	1.000	(Referent)		1.000 (Referent)			
0.01–2.85	0.579	0.276	1.217	0.438	0.179	1.068	
>2.85	0.667	0.367	1.210	0.576	0.267	1.243	
							.041

[a]Covariates: age (categorized in 3-year groups), alcohol (no/yes), diabetes (no/yes) and physical activity (no/yes).

phytochemicals which may have anti-carcinogenic actions [22]. Recent reports have examined the associations of fruit and vegetable intake on the incidence of PCa, but the findings are inconsistent and differ with the study design. Most cohort studies report non-significant results and several case-control studies suggest that vegetable intake may lower the risk of PCa [39,40]. Some authors suggested that the intakes of certain types of fruit or vegetables may be more important than others in reducing the risk of PCa, owing to the different compounds found in each [22].

Association of fish intake with PCa risk shows a statistically significant trend for reduced risk, with the >50 g category consumption in models unadjusted and adjusted for covariates ($p = .043$). Cross-national studies showed inverse associations between per capita consumption of fish and the incidence of and mortality rates from PCa [41]. Moreover, intake of fish and marine-derived ω-3 fatty acids has been shown to be associated with decreased PCa mortality [42]. A meta-analysis of fish intake and PCa [43] concluded that there was an association between fish consumption and a significant 63% reduction in PCa specific

Table 5. Odds ratios of prostate cancer aggressiveness associated with food intake.

	Unadjusted			Adjusted for covariates[a]			
	OR	95% CI Lower limit	95% CI Upper limit	OR	95% CI Lower limit	95% CI Upper limit	*p* value for trend
Fruits (g/day)							
<175	1.000	(Referent)		1.000 (Referent)			
175–350	0.667	0.222	1.998	0.890	0.269	2.939	
>350	0.353	0.106	1.178	0.360	0.100	1.299	
							.082
Vegetables (g/day)							
<64.28	1.000	(Referent)		1.000 (Referent)			
[64.28–150]	0.300	0.024	3.799	0.313	0.067	1.470	
>150	0.560	0.048	6.557	0.638	0.181	2.250	
							.162
Total fruits and vegetables (g/day)							
<297.46	1.000	(Referent)		1.000 (Referent)			
297.46–500	0.938	0.330	2.660	1.089	0.370	3.207	
>500	0.433	0.140	1.338	0.372	0.114	1.217	
							.157
Meat (g/day)							
<21.42	1.000	(Referent)		1.000 (Referent)			
21.42–64.28	1.314	0.349	4.950	0.948	0.337	2.665	
>64.28	1.440	0.269	7.714	0.711	0.130	3.879	
							.669
Legume (g/day)							
<22.85	1.000	(Referent)		1.000 (Referent)			
22.85–34.28	0.933	0.271	3.209	0.704	0.216	2.294	
>34.28	0.599	0.174	2.060	0.339	0.101	1.139	
							.351
<50.0	1.000	(Referent)		1.000			
50.0–125.0	0.822	0.221	2.143	0.604	0.312	2.131	
Dairy (g/day)							
>125.0	0.651	0.189	2.132	0.431	0.127	1.297	
							.431
Fish (g/day)							
<25	1.000	(Referent)		1.000 (Referent)			
25–50	0.818	0.276	2.422	0.702	0.265	1.856	
>50	0.630	0.168	2.360	0.389	0.099	1.527	
							.493
Hydrates (g/day)							
<30	1.000	(Referent)		1.000 (Referent)			
30–55	0.758	0.218	2.632	0.630	0.188	2.110	
>55	3.000	0.423	21.297	3.266	0.501	21.281	
							.393
Eggs (g/day)							
<17	1.000	(Referent)		1.000 (Referent)			
17–35	0.808	0.454	1.435	0.530	0.207	1.358	
>35	1.000	0.250	3.998	0.749	0.132	4.261	
							.738
Nuts (g/day)							
0	1.000	(Referent)		1.000 (Referent)			
0.01–2.85	0.571	0.167	1.952	0.639	0.158	2.592	
>2.85	1.000	0.397	2.519	0.828	0.263	2.605	
							.884

[a]Covariates: age (categorized in 3-year groups), familiar cancer (no/yes) and smoking (smoker, ex-smoker and non-smoker).

mortality (four cohort studies ($n = 49.661$), RR: 0.37; 95% CI: 0.18–0.74).

A decreased PCa risk was associated with the highest nut intake categories. When data were adjusted for covariates, there were statistically significant protective effects for high nuts intake ($p = .041$). There are few studies that analyse the role of nuts intake on prostate cancer. A small clinical study in men at risk for PCa showed increased serum γ-tocopherol and a trend towards an increase in the ratio of free prostate specific antigen (PSA): total PSA after eight weeks of a diet supplemented with 75 g walnuts per day compared with a control diet [44]. On the contrary, other study found no significant difference between mean PSA levels of a 6-month walnut-supplemented diet [45].

One of the potential reasons for inconsistent results of case-control and cohort studies examining the association between diet and PCa may be that most of the studies had a small number of advanced tumours. Given the clinical importance of advanced PCa, it is crucial to understand which nutrients, food, or food groups significantly modulate the risk of its occurrence [46]. Table 5 gives association of food consumption with PCa aggressiveness using unconditional logistic

regression model with and without adjustment of covariates. A decreased risk of aggressive PCa was associated with fruits and vegetables, legumes and fish intakes. However, these relationships were not statistically significant when data were adjusted for covariates. Epidemiological studies conducted to date have revealed that some dietary factors modulate the risk for advanced PCa [46]. It has been shown an inconsistent association for intake of fruits and vegetables with a decrease advanced PCa risk. If these findings are confirmed by more adequately powered epidemiologic studies, the risk of advanced PCa, which is fatal and thus clinically significant, may be reduced by dietary modification and chemoprevention [47].

There are some limitations of this study that must be recognized. First, although we used a validated food-frequency questionnaire for assessing the dietary intake, measurement errors that might lead to underestimation or even over estimation of associations were inevitable. In addition, PCa is a slowly growing cancer. The use of current diet as a surrogate for past diet restricts our ability to evaluate the accurate food consumption.

In conclusion, this study found an inverse association between PCa risk and the intake of fruits and vegetables, fish and nuts. The results suggested that a diet with higher intakes of these foods as Mediterranean diet may lower the risk of PCa in this population. As dietary factors are modifiable, identifying food groups or dietary patterns that modulate the risk of PCa and its aggressiveness can offer effective and practical strategies for its primary prevention.

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References

[1] Moradi Sardareh H, Goodarzi MT, Yadegar-Azari R, et al. Prostate cancer antigen 3 gene expression in peripheral blood and urine sediments from prostate cancer and benign prostatic hyperplasia patients versus healthy individuals. J Urol. 2014;11:1952–1958.
[2] Di Sebastiano KM, Mourtzakis M. The role of dietary fat throughout the prostate cancer trajectory. Nutrients. 2014;6:6095–6109.
[3] Patel VH. Nutrition and prostate cancer: an overview. Expert Rev Anticancer Ther. 2014;14:1295–1304.
[4] De Nunzio C, Presicce F, Lombardo R, et al. Physical activity as a risk factor for prostate cancer diagnosis: a prospective biopsy cohort analysis. BJU Int. 2016;117:E29–E35.
[5] Cuzick J, Thorat MA, Andriole G, et al. Prevention and early detection of prostate cancer. Lancet Oncol. 2014;15:e484–e492.
[6] Labbé DP, Zadra G, Ebot EM, et al. Role of diet in prostate cancer: the epigenetic link. Oncogene 2015;34:4683–4691.
[7] Canto P, Benitez Granados J, Martinez Ramirez MA, et al. Genetic variants in ATP6 and ND3 mitochondrial genes are not associated with aggressive prostate cancer in Mexican-Mestizo men with overweight or obesity. Aging Male. 2016;19:187–191.
[8] Grosman H, Fabre B, Mesch V, et al. Lipoproteins, sex hormones and inflammatory markers in association with prostate cancer [Research Support, Non-U.S. Gov't]. Aging Male. 2010;13:87–92.
[9] Singam P, Hong GE, Ho C, et al. Nocturia in patients with benign prostatic hyperplasia: evaluating the significance of ageing, co-morbid illnesses, lifestyle and medical therapy in treatment outcome in real life practice. Aging Male. 2015;18:112–117.
[10] Almehmadi Y, Yassin DJ, Yassin AA. Erectile dysfunction is a prognostic indicator of comorbidities in men with late onset hypogonadism. Aging Male. 2015;18:186–194.
[11] Yassin DJ, Doros G, Hammerer PG, et al. Long-term testosterone treatment in elderly men with hypogonadism and erectile dysfunction reduces obesity parameters and improves metabolic syndrome and health-related quality of life [Observational Study]. J Sex Med. 2014;11:1567–1576.
[12] Yassin A, Nettleship JE, Talib RA, et al. Effects of testosterone replacement therapy withdrawal and re-treatment in hypogonadal elderly men upon obesity, voiding function and prostate safety parameters [Research Support, Non-U.S. Gov't]. Aging Male. 2016;19:64–69.
[13] Aragón F, Perdigón G, de Moreno de LeBlanc A. Modification in the diet can induce beneficial effects against breast cancer. World J Clin Oncol. 2014;5:455–464.

[14] Lin PH, Aronson W, Freedland SJ. Nutrition, dietary interventions and prostate cancer: the latest evidence. BMC Med. 2015;13:3.
[15] Mandair D, Rossi RE, Pericleous M, et al. Prostate cancer and the influence of dietary factors and supplements: a systematic review. Nutr Metab . 2014;11:30.
[16] Comhaire F, Mahmoud A. Preventing diseases of the prostate in the elderly using hormones and nutriceuticals [Review]. Aging Male. 2004;7:155–169.
[17] Li J, Gu Z, Pan Y, et al. Dietary supplementation of alpha-linolenic acid induced conversion of n-3 LCPUFAs and reduced prostate cancer growth in a mouse model. Lipids Health Dis. 2017;16:136.
[18] Masko EM, Allott EH, Freedland SJ. The relationship between nutrition and prostate cancer: is more always better? Eur Urol. 2013;63:810–820.
[19] Perez-Cornago A, Travis RC, Appleby PN, et al. Fruit and vegetable intake and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer. 2017;141:287–297.
[20] Wu K, Spiegelman D, Hou T, et al. Associations between unprocessed red and processed meat, poultry, seafood and egg intake and the risk of prostate cancer: a pooled analysis of 15 prospective cohort studies. Int J Cancer. 2016;138:2368–2382.
[21] Arab L, Su J, Steck SE, et al. Adherence to World Cancer Research Fund/American Institute for Cancer Research lifestyle recommendations reduces prostate cancer aggressiveness among African and Caucasian Americans. Nutr Cancer. 2013;65:633–643.
[22] Meng H, Hu W, Chen Z, et al. Fruit and vegetable intake and prostate cancer risk: a meta-analysis. Asia Pac J Clin Oncol. 2014;10:133–140.
[23] Fabiani R, Minelli L, Bertarelli G, et al. A Western dietary pattern increases prostate cancer risk: a systematic review and meta-analysis [Meta-Analysis Review]. Nutrients. 2016;8:626.
[24] Schwingshackl L, Hoffmann G. Does a Mediterranean-Type Diet Reduce Cancer Risk? [Review]. Curr Nutr Rep. 2016;5:9–17.
[25] Montironi R, Santoni M, Mazzucchelli R, et al. Prostate cancer: from Gleason scoring to prognostic grade grouping. Expert Rev Anticancer Ther. 2016;16:433–440.
[26] IBM SPSS Statistics. SPSS predictive analytics software and solutions. [cited 2017 Jun 18]. Available from: http://www-01.ibm.com/software/analytics/spss/2011.
[27] Morote J, Celma A, Planas J, et al. Sedentarism and overweight as risk factors for the detection of prostate cancer and its aggressivenes. Actas Urol Esp. 2014;38:232–237.
[28] Hrafnkelsdóttir SM, Torfadóttir JE, Aspelund T, et al. Physical activity from early adulthood and risk of prostate cancer: a 24-Year follow-up study among Icelandic men. Cancer Prev Res. 2015;8:905–911.
[29] Grotta A, Bottai M, Adami HO, et al. Physical activity and body mass index as predictors of prostate cancer risk. World J Urol. 2015;33:1495–1502.
[30] Liu Y, Hu F, Li D, et al. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. Eur Urol. 2011;60:1029–1044.
[31] De Nunzio C, Albisinni S, Freedland SJ, et al. Abdominal obesity as risk factor for prostate cancer diagnosis and high grade disease: a prospective multicenter Italian cohort study. Urol Oncol. 2013;31: 997–1002.
[32] Bonn SE, Sjölander A, Tillander A, et al. Body mass index in relation to serum prostate-specific antigen levels and prostate cancer risk. Int J Cancer. 2016;139:50–57.
[33] Goktas S, Yilmaz MI, Caglar K, et al. Prostate cancer and adiponectin. Urology. 2005;65:1168–1172.
[34] Housa D, Vernerova Z, Heracek J, et al. Adiponectin as a potential marker of prostate cancer progression: studies in organ-confined and locally advanced prostate cancer [Research Support, Non-U.S. Gov't]. Physiol Res. 2008;57:451–458.
[35] Ohwaki K, Endo F, Shimbo M, et al. Comorbidities as predictors of incidental prostate cancer after Holmium laser enucleation of the prostate: diabetes and high-risk cancer. Aging Male 2017;23:1–4.
[36] Vance TM, Wang Y, Su LJ, et al. Sociodemographic, clinical, and lifestyle factors associated with prostate cancer aggressiveness in a population-based study. FASEB J. 2013;27:1061.2–1061.2.
[37] Goto K, Nagamatsu H, Teishima J, et al. Body mass index as a classifier to predict biochemical recurrence after radical prostatectomy in patients with lower prostate-specific antigen levels. Mol Clin Oncol. 2017;6:748–752.
[38] Cushen SJ, Power DG, Murphy KP, et al. Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel. Clin Nutr Espen. 2016;13:e39–e45.
[39] Aune D, De Stefani E, Ronco A, et al. Fruits, vegetables and the risk of cancer: a multisite case-control study in Uruguay. Asian Pac J Cancer Prev. 2009;10:419–428.
[40] Askari F, Parizi MK, Jessri M, et al. Fruit and vegetable intake in relation to prostate cancer in Iranian men: a case-control study. Asian Pac J Cancer Prev. 2014;15:5223–5227.
[41] Kobayashi M, Sasaki S, Hamada GS, et al. Serum n-3 fatty acids, fish consumption and cancer mortality in six Japanese populations in Japan and Brazil. Jpn J Cancer Res. 1999;90:914–921.
[42] Chavarro JE, Stampfer MJ, Hall MN, et al. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. Am J Clin Nutr. 2008;88:1297–1303.
[43] Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr. 2010;92:1223–1233.
[44] Spaccarotella KJ, Kris-Etherton PM, Stone WL, et al. The effect of walnut intake on factors related to prostate and vascular health in older men. Nutr J. 2008;7:13.
[45] Simon JA, Tanzman JS, Sabaté J. Lack of effect of walnuts on serum levels of prostate specific antigen: a brief report. J Am Coll Nutr. 2007;26:317–320.
[46] López-Guarnido O, Alvarez-Cubero MJ, Saiz M, et al. Bioactive compounds of the Mediterranean diet and prostate cancer. J Nutr Health Aging.
[47] Gathirua-Mwangi WG, Zhang J. Dietary factors and risk for advanced prostate cancer. Eur J Cancer Prev. 2014;23:96–109.