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Mediterranean dietary pattern is associated to low risk of aggressive prostate cancer: MCC-Spain study

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TITLE: Mediterranean dietary pattern is associated to low risk of aggressive prostate cancer: MCC-Spain study.

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ABSTRACT

Purpose: To explore the association of the previously described Western, Prudent and Mediterranean dietary patterns with prostate cancer risk by tumor aggressiveness and extension.

Methods: MCC-Spain is a population-based multicase-control study, carried out in 7 Spanish provinces between September 2008 and December 2013. It collected anthropometric, epidemiologic and dietary information on 754 histologically confirmed incident cases of prostate cancer and 1277 controls aged 38 to 85 years. Three previously identified dietary patterns –Western, Prudent and Mediterranean- were reconstructed using MCC-Spain data. The association between each pattern and prostate cancer risk was assessed using logistic regression models with random province-specific intercepts. Risk according to tumor aggressiveness (Gleason score grade =6 vs >6) and extension (cT1-cT2a vs cT2b-cT4) was evaluated with multinomial regression models.

Results: High adherence to Mediterranean dietary pattern -rich in fruits and vegetables, but also in fish, legumes and olive oil- was specifically associated to lower risk of prostate cancer with Gleason score >6: $RRR_{Quartile3(Q3)vsQuartile1(Q1)}$=0.66; 95%CI:0.46-0.96 and $RRR_{Quartile4(Q4)vsQuartile1}$=0.68;95%CI:0.46-1.01;p-trend=0.023) or with higher clinical stage (cT2b-T4: $RRR_{Quartile4vsQuartile1}$=0.49; 95%CI:0.25-0.96; p-trend=0.024). This association was not observed with Prudent pattern, which combines vegetables and fruits with low fat dairy products, whole grains and juices. Western pattern did not show any association with prostate cancer risk.

Conclusions: Nutritional recommendations for prostate cancer prevention should consider whole dietary patterns instead of individual foods. We found important differences between Mediterranean dietary pattern, which was associated to lower risk of aggressive prostate cancer, and Western and Prudent dietary patterns, that had no relationship with prostate cancer risk.

INTRODUCTION

Prostate cancer (PC) represents the most common type of cancer among males in Europe and the third with the highest mortality[1] but its etiology is not well understood. There is only limited evidence linking PC to specific environmental, occupational and dietary exposures[2], which might be in part associated to the confounding effect of detection by screening with prostate specific antigen (PSA). This test detects many low grade indolent tumors that would otherwise remained undiagnosed and which may represent a different clinical entity than high grade PC, with different risk profiles[3]. The association of diet and PC is also unclear. According to the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) report[3], there is limited evidence of a detrimental effect of a high consumption of dairy products and other foods rich in calcium, and low levels of selenium and alpha-tocopherol on PC. Even though, these patterns capture both, the variability in the population's diet and the possible interactions between individual dietary factors[4], a scarce number of studies explore the association between overall dietary patterns and PC risk. While some of them report a positive association between a high adherence to the Western dietary pattern[5-9] and PC risk, others show no association[9-13]. On the other hand, some studies show a protective effect of diets with elevated consumption of vegetables, fruit[14] and fish[6] but most do not find any association with Prudent/Healthy/Mediterranean dietary patterns[5, 7-13].

A recent publication identified three dietary patterns in Spanish women[15]: a Western pattern associated with increased risk of breast cancer (BC), a Prudent pattern not associated with this tumor, and a protective Mediterranean dietary pattern. This study was the first identifying these two last dietary patterns in the same population with data reduction statistical methods. Mediterranean and Prudent dietary patterns, which are commonly interchanged in the bibliography, present individual characteristics that might be behind their

differential effect on BC risk[15]. The Prudent dietary pattern (high consumption of low fat dairy products, vegetables, fruits, whole grains and juices) might correspond to participants concerned about their weight, while those following a Mediterranean dietary pattern (high intake of fruits and vegetables but also of fish, legumes, boiled potatoes, olives and vegetable oil, and a low intake of juices) seemed to be less worried about fat intake. This differential effect on BC, also found in an independent sample[16], suggests that fruits and vegetables consumption might not be enough to lower cancer risk, at least for BC. It is especially relevant to test whether this also applies to PC, which shows epidemiological, biological, genetic and aetiopathogenic similarities with BC risk[17].

Our aim is to explore, in MCC-Spain case-control study, whether there is any association between these three dietary patterns and PC risk, taking into account tumor aggressiveness and extension.

MATERIAL AND METHODS

MCC-Spain

The population-based multicase-control study MCC-Spain[18, 19] recruited, between September 2008 and December 2013, histologically confirmed incident cases of five tumors (breast, prostate, colorectal, gastric and chronic lymphocytic leukemia) and a single set of population-based controls, frequency matched by age and sex with the overall distribution of cases for each province. Inclusion criteria required that participants were 20-85 years old, were able to answer the questionnaire, and resided for at least 6 months in the study areas. Cases were identified and invited to participate in person as soon as possible after the diagnosis through active search, including periodical visits to the collaborating hospitals. Population-based controls, randomly selected from general practitioner lists of primary care health centers of

the catchment area of each collaborating hospital, were contacted by phone. Those who agreed to participate answered a structured computerized epidemiological questionnaire administered by trained personnel in a face-to-face interview to gather information on socio-demographic and lifestyle factors, personal/family medical history and self-reported height and weight. Diet on the previous year was assessed with a 154-items semi-quantitative food frequency questionnaire (FFQ), modified from a previously validated instrument in Spain[20] to include regional products. The FFQ was handed in when cases and controls were recruited, filled at home and returned by mail.

For PC (International Classification of Diseases 10th Revision: C61, D07.5) we included those cases with no prior history of the disease and diagnosed within the recruitment period in 14 hospitals of 7 Spanish provinces (Madrid, Barcelona, Asturias, Huelva, Cantabria, Valencia, Granada). Since MCC-Spain is a multi-objective study, sample size was prefixed: for PC, 1000 cases were the initial objective and 1112 were finally recruited. Controls with personal history of PC, from provinces that had not recruited PC cases and, within each province, those more than 5 years younger than the youngest PC case were excluded. Response rates were 52.2% for controls and 67.4% for PC cases[19]. We excluded 23 PC cases with Gleason <6. Of the 1090 remaining cases of and 1493 recruited controls, 952 cases and 1311 controls returned the FFQ and reported energy intakes from 750-4500 kcal/day. Cases providing dietary information more than 6 months after diagnosis (n=198) and controls with previous prostate adenoma surgery (n=34) were excluded. Therefore, 754 PC cases and 1277 controls were included in the study. Data on body mass index (BMI) or total energy intake (due to incomplete FFQ) was missing for 21 cases and 48 controls; hence, multivariable analyses were carried out over 733 cases and 1229 controls (See Figure 1).

Histopathological information was extracted from hospital clinical records using a standardized form (supplementary material, Table S1).

The protocol of MCC-Spain was approved by the Ethics Committee of all collaborating institutions, and each participant signed an informed consent form.

Dietary patterns

We evaluated the adherence to three dietary patterns previously identified in the control population of a multicentric BC case-control study (EpiGEICAM) in our country[15]: A Western dietary pattern, positively associated with BC risk, and characterized by high intakes of high-fat dairy products, refined grains, processed meat, caloric drinks, sweets, convenience food and sauces and by low intakes of low-fat dairy products and whole grains; a Prudent pattern, not related to BC, which reflected high intake of low-fat dairy products, whole grains, vegetables, fruits and juices; and a Mediterranean dietary pattern, that seemed to be protective for BC, representing high intake of fish, boiled potatoes, vegetables, legumes, fruits, vegetable oil and olives –in our context mostly olive oil (71%) and olives (23%)- and low intake of juices. To identify these patterns, the items from the EpiGEICAM FFQ were grouped into 26 inter-correlated food groups that were log-transformed and centered. Afterwards, principal components analysis without rotation of the variance-covariance matrix was applied. The obtained set of weights (pattern loadings) represent the correlation between the consumption of each food group and the component/pattern scores[21], and can be used to apply such patterns in other populations[22]. In MCC-Study, we grouped the FFQ items, excluding non-caloric and alcoholic beverages, into the same 26 food groups (Supplementary Material, **Table S2**) and calculated the score of adherence to the Western, Prudent and Mediterranean dietary patterns as a linear combination of the weights of each food group and pattern published in the EpiGEICAM study[15] and the log-transformed centered food group consumption reported by the participants of MCC-Spain. These scores of adherence were grouped into quartiles of their distribution among controls.

Following the description of the sample characteristics, the association between the adherence to each dietary pattern and PC risk was evaluated using mixed logistic regression models with random province-specific intercepts. After considering the most important confounders published in the literature, we kept in the models caloric intake, BMI, age, education and family history of PC.

We also studied the relationship between the adherence to these patterns and PC by tumor aggressiveness defining two dependent variables with three categories: a) based on Gleason score at diagnosis[23] (control, low grade (=6), and high grade (>6), and b) based on the clinical extension of the tumor (control, cT1-cT2a, cT2b-T4)[24]. Afterwards, we fitted specific multinomial logistic regression models for each dependent variable and dietary pattern. These models were adjusted by caloric intake, BMI, age, education, family history of PC and province of residence as fixed effects. Heterogeneity of effects was tested using a Wald test. The p-value for trend was calculated with the Wald test, including in the models the variables that define the quartiles of adherence as continuous. Sensitivity analyses also considered the International Society of Urological Pathology (ISUP) grading[23], PSA at diagnosis and American Joint Committee on Cancer (AJCC) 8th edition stage[24] (supplementary material, Table S3).

Analyses were performed using STATA/MP (version 14.1, 2015, StataCorp LP) and statistical significance was set at 2-sided $p < 0.05$.

RESULTS

No differences in the score of adherence to the Western, Prudent and Mediterranean dietary patterns were observed between cases and controls in the bivariate analyses. Compared to controls, PC cases were less educated and more physically active, reported higher alcohol intake and had more relatives with PC (**Table 1)**.

Table 2 summarizes the adjusted odds ratios (aORs) and relative risk ratios (aRRRs) for the association between the scores of adherence to the three dietary patterns and PC incidence, for the whole sample, by tumor aggressiveness and by extension. None of the dietary patterns showed association with total PC risk, but Prudent and Mediterranean dietary patterns showed different effects in low and high grade tumors ($p\text{-het}_{prudent}$=0.019; $p\text{-het}_{Mediterranean}$=0.026). Higher adherence to the Prudent pattern seemed to be associated to a higher risk of low grade tumors, although the trend was not statistically significant (p-trend=0.234). In contrast, we observed a clear inverse association between adherence to the Mediterranean dietary pattern and risk of aggressive tumors, both according to Gleason score (Gleason>6:$aRRR_{Q3sQ1}$=0.66; 95%CI:0.46-0.96 and $aRRR_{Q4vsQ1}$=0.68; 95%CI:0.46-1.01; p-trend=0.023) and by tumor extension (cT2b-T4: $aRRR_{Q4vsQ1}$=0.49; 95%CI:0.25-0.96; p-trend=0.024), although in this last case the p-value for heterogeneity was not statistically significant (p-het=0.250), probably due to the low number of advanced PC. Results were similar when other clinical classifications of tumors were used (supplementary material, table S3). Regarding Western dietary pattern, our data hint that a high adherence to this pattern might increase the risk of high extension prostate tumors, although neither the risk estimators nor the test for trend achieved statistical significance.

DISCUSSION

Our results show that the association between dietary patterns and PC risk differs by tumor aggressiveness, suggesting that high adherence to a Mediterranean diet could have a protective effect against more aggressive and more advanced PC. In contrast, there was not any clear relationship between adherence to Prudent and Western diet and PC risk.

Most of the studies exploring the association between the adherence to data driven dietary patterns and PC risk identify one or various patterns correlated with a high

consumption of fruits and vegetables named Healthy/Prudent/Conscious/Vegetarian[5, 7-14], that in some instances also include foods characteristic of the Mediterranean dietary pattern such as fish[6, 9], legumes[6, 10] or vegetable oils[6, 9]. Only a few of these studies reported a possible protective effect of diets with elevated consumption of vegetables and fruits[14] and fish and olive oil[6, 25] while most of them did not find any effect[5, 7-13, 26]. However, a protective effect of Healthy/Prudent/Mediterranean diets was clearly seen for aggressive tumors (Gleason>6)[5, 11, 14].

In this study we have found that Prudent and Mediterranean dietary patterns have different associations with PC risk. Also, our results indicate that the possible preventive effect of a Mediterranean diet is specific of aggressive PC, defined as cases with Gleason >6 or cT2b-T4, suggesting a certain role of some of its dietetic components in the progression of the disease. Some nutrients present in, Prudent and Mediterranean diets, such as lycopene or tomato sauce, seem to reduce risk of PC recurrence/progression[27]. However, foods and nutrients that differ between them -mainly fish and dairy- present different relationships with PC evolution. In this sense, a metaanalysis reported no effect of fish intake (characteristic of the Mediterranean dietary pattern) on PC incidence but a clear protective effect against PC-specific mortality[25]. Fish oil also reduces prostate tumor growth and histopathological progression in animal models[28]. In contrast high consumption of dairy products, only present in the Prudent pattern, increases risk of advanced, metastatic, or fatal PC[3, 27].

The majority of previous studies also identify a Western pattern, that usually includes a high consumption of red and/or processed meat and energy dense foods[5-8, 10-13] and, sometimes, an elevated intake of eggs[7] and refined grains[7, 9]. Results on Western dietary pattern and PC are contradictory, with a similar number of authors claiming a positive[5-9] and a null[9-13] association, but usually showing a stronger detrimental effect for advanced PC[5, 10]. A recent metaanalysis[26] supports the hypothesis of a pernicious effect of a high adherence to this

pattern on PC risk. Our results also point in this direction although they do not achieve statistical significance.

As mentioned before, our Western, Prudent and Mediterranean dietary patterns were obtained over the control population of the EpiGEICAM multicentric case-control study on female BC in Spain[15] and their reproducibility was afterwards assessed in a different sample of 3500 Spanish healthy women[29]. In this case, given the shared characteristics of breast and prostate tumors[17], we applied the original scoring system even though our participants were Spanish males. A previous study showed that scores of adherence to dietary patterns can be calculated with the exact same rules over different populations, resulting in different levels of adherence but still being valid[22].

Some possible confounders and interactions were also explored. Firstly, even though the last report of the WCRF/AICR[3] does not include alcohol intake among PC risk factors, as there was different ethanol intake between cases and controls , models were adjusted by ethanol intake, obtaining similar results (supplementary material, table S4). Secondly, the possible synergic effect of the dietary patterns with age, BMI, family history of prostate cancer, alcohol intake and smoking was also tested and no significant heterogeneity was found (supplementary material, table S5). Finally, other classifications of tumors and stratifications were also considered in the sensitivity analysis, finding similar associations for the most aggressive tumors (supplementary material, table S3).

Our results should be interpreted in the context of the study limitations. Differential recall bias is always a relevant concern in case-control studies, especially when evaluating the effect of self-reported information. Anticipating this problem, some questions about general dietary habits were used to adjust the responses to the FFQ following the methodology described in Calvert et al.[30]. In addition, only cases that responded to the questionnaire within

the 6 months following the diagnosis were included. On the other hand, this study has several strengths. We recruited histologically confirmed cases of PC and population-based controls. The wide geographical variability of the recruited participants, coming from 7 provinces located throughout the Spanish geography, ensured the representation of the different diets coexisting within Spain. Finally, the sample size allowed the exploration of the associations by tumor aggressiveness and extension of the primary tumor using different classifications and obtaining very congruent results.

CONCLUSIONS

Mediterranean diet, rich in fruits and vegetables, but also in fish, legumes and olive oil- could help preventing aggressive PC tumors. Dietary recommendations should take into account whole patterns instead of focusing on individual foods.

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FIGURE LEGEND:

Figure 1: Flow chart displaying the selection process of prostate cancer cases and controls. MCC-Spain study 2008–2013.

Table 1. Distribution of scores of adherence to Western, Prudent and Mediterranean dietary patterns and other baseline characteristics for prostate cancer cases and controls.

	Controls	Cases	p[a]
	n=1277	n=754	
Dietary Patterns			
Western mean(SD)	0.26 (3.53)	0.56 (3.34)	0.063[a]
Prudent mean(SD)	-0.43 (3.56)	-0.38 (3.46)	0.751[a]
Mediterranean mean(SD)	-0.04 (3.18)	-0.05 (2.94)	0.934[a]
Energy intake (kcal/day) mean(SD)	2018 (607)	2068 (616)	0.079[a]
Alcohol (g/day) median(IQR)	19 (6;42)	22 (8;45)	0.010[b]
Age (years) mean(SD)	66 (9)	66 (7)	0.111[a]
Education n(%)			<0.001[c]
No formal Education	227 (18%)	169 (22%)	
Primary School	421 (33%)	296 (39%)	
Secondary School	359 (28%)	165 (22%)	
University or more	270 (21%)	124 (16%)	
BMI (kg/m2) mean(SD)	27.50 (3.79)	27.68 (3.79)	0.305[a]
Physical Activity (METs-hours/week)[d] n(%)			0.008[c]
0 METs/week	518 (41%)	287 (38%)	
0.1-7.9 METs/week	160 (13%)	99 (13%)	
8.0-15.9 METs/week	144 (11%)	100 (13%)	
>=16 METs/week	436 (34%)	268 (36%)	
Unknown	19 (1%)	0 (0%)	
Family history of PC n(%)			<0.001[c]
No	1182 (93%)	598 (79%)	
2nd Degree	16 (1%)	21 (3%)	
One of 1st degrees	76 (6%)	116 (15%)	
More than one of 1st degree	3 (0%)	19 (3%)	

[a] The p-value was calculated with the Student t-test for comparison of independent means.

[b] The p-value was calculated with the Wilcoxon rank-sum test.

[c] The p-value was calculated with the Chi-square test.

[d] Cut points defined according to the 2008, Physical Activity Guidelines for Americans (https://health.gov/paguidelines/).

Table 2. Adjusted odds ratios (OR) and relative risk ratios (RRR) for the association between prostate cancer incidence and the scores of adherence to Western, Prudent and Mediterranean dietary patterns by tumor aggressiveness and extension.

			ALL		GLEASON=6		GLEASON>6			cT1-cT2a		cT2b-T4	
			n=733		n=333[b]		n=388[b]			n=578[c]		n=109[c]	
	Co[a]	Ca[a]	aOR[d](95%CI)	Ca[a]	aRRR[d](95%CI)	Ca[a]	aRRR[d](95%CI)	p-het	Ca[a]	aRRR[d](95%CI)	Ca[a]	aRRR[d](95%CI)	p-het
WESTERN								0.957[e]					0.541[e]
Q1[a]	301	162	1	66	1	93	1		130	1	24	1	
Q2[a]	314	182	1.11 (0.84;1.48)	82	1.20 (0.82;1.75)	97	1.07 (0.75;1.51)		149	1.14 (0.84;1.54)	25	1.08 (0.59;1.99)	
Q3[a]	307	187	1.19 (0.88;1.59)	88	1.28 (0.87;1.89)	98	1.15 (0.80;1.66)		147	1.15 (0.84;1.57)	27	1.27 (0.68;2.36)	
Q4[a]	307	202	1.15 (0.83;1.58)	97	1.18 (0.78;1.81)	100	1.11 (0.75;1.65)		152	1.05 (0.74;1.49)	33	1.56 (0.81;3.02)	
p-trend			0.361[f]		0.415[f]		0.535[f]			0.774[f]		0.164[f]	
PRUDENT								0.019[e]					0.644[e]
Q1[a]	299	176	1	57	1	114	1		140	1	32	1	
Q2[a]	310	175	0.95 (0.71;1.25)	83	1.33 (0.90;1.96)	90	0.78 (0.55;1.09)		138	0.92 (0.68;1.24)	23	0.76 (0.42;1.35)	
Q3[a]	315	200	1.06 (0.80;1.41)	104	1.60 (1.09;2.36)	93	0.80 (0.56;1.13)		162	1.05 (0.78;1.42)	25	0.82 (0.46;1.48)	
Q4[a]	305	182	0.94 (0.69;1.28)	89	1.29 (0.85;1.97)	91	0.78 (0.54;1.14)		138	0.86 (0.62;1.21)	29	0.96 (0.51;1.78)	
p-trend			0.924[f]		0.180[f]		0.215[f]			0.605[f]		0.912[f]	
MEDITERRANEAN								0.026[e]					0.250[e]
Q1[a]	301	189	1	66	1	118	1		145	1	36	1	
Q2[a]	312	196	1.00 (0.76;1.31)	87	1.24 (0.85;1.81)	105	0.87 (0.63;1.21)		152	1.00 (0.74;1.34)	32	0.92 (0.54;1.56)	
Q3[a]	314	161	0.86 (0.64;1.16)	85	1.27 (0.86;1.88)	76	0.66 (0.46;0.96)		132	0.92 (0.67;1.27)	21	0.63 (0.34;1.17)	
Q4[a]	302	187	0.90 (0.66;1.23)	95	1.31 (0.86;1.99)	89	0.68 (0.46;1.01)		149	0.94 (0.67;1.32)	20	0.49 (0.25;0.96)	
p-trend			0.361[f]		0.240[f]		0.023[f]			0.628[f]		0.024[f]	

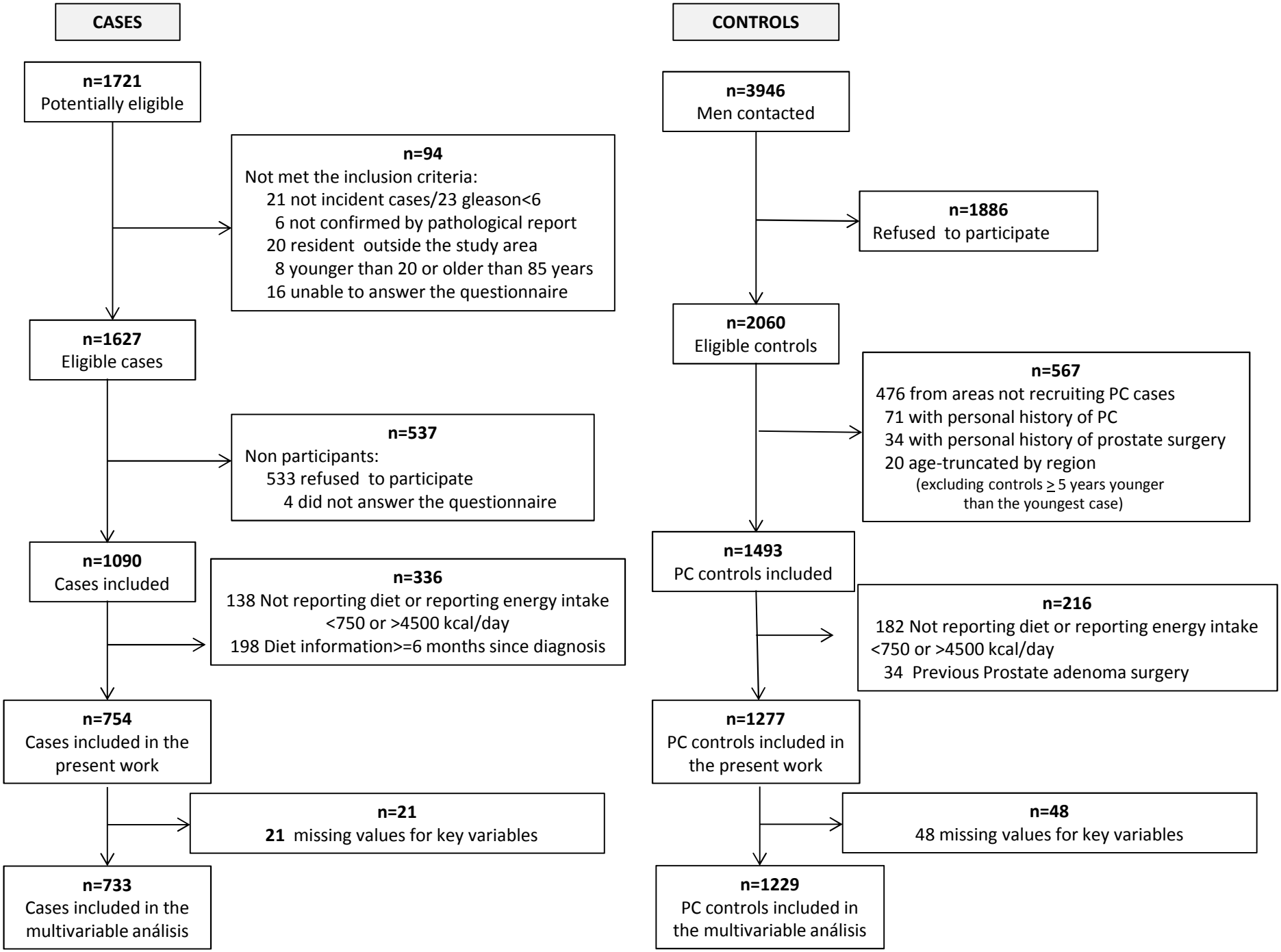
[a] Co: Controls; Ca: Cases; Q(1, 2, 3, 4): Quartile (1, 2, 3, 4)

[b] 12 cases with complete information on all the covariables did not have Gleason Score.

[c] 46 cases with complete information on all the covariables did not have information on clinical stage.

[d] Adjusted by age, education, BMI, family history of prostate cancer and caloric intake as fixed effects and province of residence as a random effect.

[e] The p-value from heterogeneity of effects was calculated with the Wald test to assess if the coefficients are equal to each other for all categories of the dependent variable.
[f] The p-value for trend was calculated with the Wald test, including in the models the variables that define the quartiles of adherence as continuous



Key Definitions for Abbreviations

PC: prostate cancer.

PSA: prostate specific antigen.

WCRF/AICR: World Cancer Research Fund and the American Institute for Cancer Research.

BC: Breast Cancer.

MCC-Spain: Multicase-Control study on Common tumors in Spain.

FFQ: food frequency questionnaire.

BMI: body mass index.

EpiGEICAM: Epidemiological study of the Spanish Group for Breast Cancer Research (Grupo Español de Investigación en Cáncer de Mama).

ISUP: International Society of Urological Pathology.

AJCC :American Joint Committee on Cancer.

aOR: adjusted odds ratio.

aRRR: adjusted relative risk ratio.

p-het: p value for heterogeneity of effects.

p-trend: p value for trend.

Table S1: Clinical profile of PC cases: Total number and percentages of tumor classification according to Gleason Score (biopsy), ISUP grading, PSA at diagnosis and AJCC stage (8th edition).

GLEASON score (biopsy)		n	%
	6	337	44.69
	7	310	41.11
	8	57	7.56
	9	37	4.91
	10	1	0.13
	Unknown	12	1.59
Clinical Stage		n	%
	cT1b	2	0.27
	cT1c	462	61.27
	cT2a	77	10.21
	cT2b	50	6.63
	cT2c	79	10.48
	cT3a	25	3.32
	cT3b	8	1.06
	cT4	1	0.13
	Unknown	50[a]	6.63
ISUP Grading		n	%
	1	337	44.69
	2	224	29.71
	3	85	11.27
	4	57	7.56
	5	38	5.04
	Unknown	13	1.72
PSA at diagnosis		n	%
	<10	557	73.87
	10-20	145	19.23
	>20	47	6.23
	Unknown	5[a]	0.66
AJCC stage (8th edition)		n	%
	I	268	35.54
	IIA	59	7.82
	IIB	198	26.26
	IIC	111	14.72
	IIIA	26	3.45
	IIIB	19	2.52
	IIIC	36	4.77
	IV A	3	0.4
	IV B	8	1.06
	Unknown	26[a]	3.45

[a] The number of missing values on clinical stage, PSA and AJCC stage (8th Edition) reported here is higher than the numbers reported in the footnotes from table S3, because such table only consider cases with complete information on all the covariables included in the models

Table S2: Composition of food groups based on the food frequency questionnaire of the MCC-Spain study and component loadings for each pattern identified in the EpiGEICAM study[1].

FOOD GROUP	FOOD[a]	W[b]	P[b]	M[b]
HIGH-FAT DAIRY	Whole-fat milk, condensed milk, whole-fat yogurt, semi-cured, cured, or creamy cheese, blue cheese, custard, milk shake, ice-cream, double cream.	0.60	-0.11	0.20
LOW-FAT DAIRY	Semi-skimmed and skimmed milk, soy milk, skimmed yogurt, curd, cottage or fresh white cheese.	-0.49	0.60	-0.01
EGGS	Eggs.	0.19	0.08	0.16
WHITE MEAT	Chicken, rabbit and duck.	0.08	0.17	0.18
RED MEAT	Pork, beef, lamb, liver (beef, pork or chicken), entrails, hamburgers (pork or beef) and meatballs (pork or beef).	0.27	0.09	0.22
PROCESSED MEAT	Sausages, serrano ham and other cold meat, bacon, pâte, foie-gras.	0.36	0.10	0.26
WHITE FISH	Fresh or frozen white fish (hake, sea bass, sea bream), ½·salted fish and ½·smoked fish.	0.01	0.24	0.34
OILY FISH	Fresh or frozen blue fish (tuna, swordfish, sardines, anchovies, salmon), canned fish, ½·salted fish and ½·smoked fish.	0.05	0.24	0.44
SEAFOOD/SHELLFISH	Clams, mussels, oysters, squid, cuttlefish, octopus, prawn, crab, shrimp and similar products.	0.17	0.27	0.35
LEAFY VEGETABLES	Spinach, chard, lettuce and other leafy vegetables.	-0.11	0.34	0.40
FRUITING VEGETABLES	Tomato, eggplant, zucchini, cucumber, pepper, artichoke and avocado.	0.00	0.36	0.45
ROOT VEGETABLES	Carrot, pumpkin and radish.	0.05	0.35	0.44
OTHER VEGETABLES	Cooked cabbage, cauliflower or broccoli, onion, green beans, asparagus, mushrooms, corn, garlic, gazpacho, vegetable soup and other vegetables.	-0.04	0.40	0.42
LEGUMES	Peas, lentils, chickpeas, beans and broad beans.	0.21	0.15	0.34
POTATOES	Roasted or boiled potatoes and sweet potatoes.	0.17	0.25	0.40
FRUITS	Orange, grapefruit, mandarin, banana, apple, pear, grapes, kiwi, strawberries, cherries, peach, figs, melon or watermelon, prunes, mango and papaya and other fresh or dried fruits.	-0.07	0.31	0.31
NUTS	Almonds, peanuts, pine nuts, hazelnut	0.18	0.22	0.29
REFINED GRAINS	White-flour bread, rice, pasta	0.37	0.15	0.23
WHOLE GRAINS	Whole-grain bread and breakfast cereals	-0.43	0.47	-0.06
OLIVES AND VEGETABLE OIL	Olives, added olive oil to salads, bread and dishes, other vegetable oils (sunflower, corn, soybean).	0.12	0.19	0.34
OTHER EDIBLE FATS	Margarine, butter and lard.	0.22	0.02	0.11
SWEETS	Chocolate and other sweets, cocoa powder, plain cookies, chocolate cookies, pastries (croissant, donut, cake, pie or similar)	0.35	0.18	0.05
SUGARY	Jam, honey, sugar and fruit in sugar syrup.	0.24	0.05	0.00
JUICES	Tomato juice, freshly squeezed orange juice, juice (other than freshly squeezed)	0.25	0.67	-0.39
CALORIC DRINKS	Sugar-sweetened soft drinks and nut milk.	0.74	0.21	-0.25
CONVENIENCE FOOD AND SAUCES	Croquette, fish sticks, dumplings, kebab, fried potatoes, crisps, pizza, instant soup, mayonnaise, tomato sauce, hot sauce, ketchup and other sauces.	0.47	0.12	0.24

[a] Log-transformed centered intake in grams. [b] W: Western; P: Prudent; M: Mediterranean

Table S3. Adjusted relative risk ratios (aRRR) for the association between prostate cancer incidence and the scores of adherence to Western, Prudent and Mediterranean dietary patterns by ISUP grading[2], PSA at diagnosis and American Joint Committee on Cancer 8th edition (*AJCC*) stage[3].

		ISUP grading					PSA at diagnosis					AJCC stage (8th ed)				
		1+2		3+4+5			<10		>=10			I-IIA		IIB-IV		
	Co[a]	Ca[a] n=546[b]	aRRR[e] (95%CI)	Ca[a] n=174[b]	aRRR[e] (95%CI)	p-het	Ca[a] n=544[c]	aRRR[e] (95%CI)	Ca[a] n=185[c]	aRRR[e] (95%CI)	p-het	Ca[a] n=324[d]	aRRR[e] (95%CI)	Ca[a] n=386[d]	aRRR[e] (95%CI)	p-het
WESTERN						0.889					0.628					0.661
Q1[a]	301	118	1	41	1		116	1	45	1		62	1	97	1	
Q2[a]	314	137	1.14 (0.84;1.56)	42	1.05 (0.65;1.69)		137	1.16 (0.84;1.58)	45	1.05 (0.66;1.66)		80	1.26 (0.85;1.85)	98	1.03 (0.73;1.45)	
Q3[a]	307	142	1.23 (0.89;1.69)	43	1.11 (0.68;1.82)		142	1.23 (0.89;1.70)	44	1.10 (0.68;1.78)		89	1.41 (0.95;2.08)	94	1.05 (0.73;1.51)	
Q4[a]	307	149	1.12 (0.78;1.59)	48	1.21 (0.71;2.05)		149	1.10 (0.77;1.56)	51	1.31 (0.78;2.20)		93	1.25 (0.82;1.92)	97	1.03 (0.69;1.53)	
p-trend			0.487		0.464			0.573		0.308			0.275		0.867	
PRUDENT						0.455					0.666					0.058
Q1[a]	299	122	1	49	1		127	1	49	1		60	1	115	1	
Q2[a]	310	136	1.06 (0.78;1.45)	37	0.72 (0.45;1.16)		136	0.99 (0.72;1.34)	39	0.83 (0.52;1.33)		79	1.20 (0.82;1.77)	91	0.78 (0.56;1.10)	
Q3[a]	315	151	1.16 (0.85;1.60)	46	0.86 (0.54;1.37)		144	1.02 (0.74;1.39)	54	1.17 (0.75;1.84)		99	1.45 (0.99;2.13)	93	0.79 (0.56;1.12)	
Q4[a]	305	137	1.03 (0.73;1.45)	42	0.75 (0.45;1.25)		137	0.93 (0.66;1.30)	43	0.95 (0.57;1.58)		86	1.19 (0.78;1.81)	87	0.75 (0.51;1.09)	
p-trend			0.739		0.389			0.721		0.797			0.309		0.147	
MEDITERRANEAN						0.435					0.950					0.069
Q1[a]	301	139	1	45	1		140	1	49	1		68	1	119	1	
Q2[a]	312	143	1.00 (0.74;1.36)	49	1.01 (0.64;1.59)		148	0.98 (0.72;1.33)	47	1.03 (0.65;1.62)		86	1.18 (0.81;1.72)	105	0.87 (0.63;1.22)	
Q3[a]	314	121	0.91 (0.66;1.26)	40	0.81 (0.49;1.32)		120	0.84 (0.61;1.17)	40	0.93 (0.57;1.51)		80	1.17 (0.79;1.73)	75	0.66 (0.46;0.95)	
Q4[a]	302	143	0.99 (0.70;1.40)	40	0.66 (0.39;1.14)		136	0.86 (0.60;1.21)	49	1.00 (0.60;1.68)		90	1.19 (0.78;1.81)	87	0.67 (0.45;0.99)	
p-trend			0.844		0.095			0.273		0.913			0.485		0.019	

[a] Co: Controls; Ca: Cases; Q(1, 2, 3, 4): Quartile (1, 2, 3, 4)

[b] 13 cases with complete information on all the covariables did not have information on ISUP grading.

[c] 4 cases with complete information on all the covariables did not have information on PSA.

[c] 23 cases with complete information on all the covariables did not have information on AJCC stage (8th edition).

[e] Adjusted by age, education, BMI, family history of prostate cancer and caloric intake as fixed effects and province of residence as a random effect.

Table S4 Adjusted odds ratios (aOR) and relative risk rations (aRRR) for the association between prostate cancer incidence and the scores of adherence to Western, Prudent and Mediterranean dietary patterns by tumor aggressiveness and extension including alcohol as a confounder.

		ALL n=733		GLEASON=6 n=333[a]		GLEASON>6 n=388[a]			cT1-cT2a n=578		cT2b-T4 n=109		
	Controls	Cases	aOR(95%CI)	Cases	aRRR(95%CI)	Cases	aRRR(95%CI)	p-het	Cases	aRRR(95%CI)	Cases	aRRR(95%CI)	p-het
WESTERN								0.531					0.531
Q1	302	162	1	66	1	93	1		130	1	24	1	
Q2	314	182	1.12 (0.84;1.49)	82	1.20 (0.82;1.74)	97	1.08 (0.77;1.54)		149	1.14 (0.84;1.55)	25	1.10 (0.60;2.02)	
Q3	306	187	1.20 (0.89;1.61)	88	1.29 (0.87;1.90)	98	1.18 (0.82;1.69)		147	1.16 (0.85;1.59)	27	1.30 (0.69;2.42)	
Q4	307	202	1.16 (0.84;1.60)	97	1.18 (0.78;1.80)	100	1.13 (0.76;1.68)		152	1.06 (0.75;1.50)	33	1.59 (0.82;3.08)	
p-trend			0.333		0.416		0.476			0.738		0.147	
PRUDENT								0.642					0.642
Q1	300	176	1	57	1	114	1		140	1	32	1	
Q2	310	175	0.96 (0.72;1.27)	83	1.33 (0.90;1.96)	90	0.80 (0.57;1.12)		138	0.93 (0.68;1.25)	23	0.78 (0.44;1.41)	
Q3	314	200	1.09 (0.82;1.46)	104	1.61 (1.09;2.38)	93	0.84 (0.59;1.19)		162	1.08 (0.79;1.46)	25	0.87 (0.48;1.58)	
Q4	305	182	0.97 (0.71;1.33)	89	1.30 (0.85;1.98)	91	0.83 (0.56;1.21)		138	0.89 (0.63;1.24)	29	1.03 (0.55;1.93)	
p-trend			0.903		0.181		0.372			0.727		0.896	
MEDITERRANEAN								0.277					0.277
Q1	301	189	1	66	1	118	1		145	1	36	1	
Q2	312	196	1.01 (0.76;1.33)	87	1.24 (0.85;1.80)	105	0.89 (0.64;1.25)		152	1.01 (0.75;1.36)	32	0.95 (0.55;1.61)	
Q3	314	161	0.87 (0.65;1.17)	85	1.26 (0.85;1.87)	76	0.68 (0.47;0.99)		132	0.93 (0.68;1.28)	21	0.65 (0.35;1.21)	
Q4	302	187	0.91 (0.66;1.25)	95	1.31 (0.86;1.99)	89	0.70 (0.48;1.04)		149	0.95 (0.68;1.34)	20	0.51 (0.26;1.00)	
p-trend			0.41		0.249		0.036			0.677		0.031	

[a] 12 cases did not have information about the Gleason Score.
[b] 46 cases did not have information on cT
[c] Adjusted by age, education, BMI, family history of prostate cancer and caloric intake as fixed effects and province of residence as a random effect.

Table S5: Summary of p-values for the test of the interaction of age, BMI, family history of prostate cancer, alcohol intake and smoking habit with the quartiles of adherence to the Western, Prudent and Mediterranean dietary patterns in the multinomial model that include the Gleason classification as the dependent variable (0=Control; 1:Gleason =6; 2=Gleason>6)

	WESTERN	PRUDENT	MEDITERRANEAN
Age (years)	0.212	0.807	0.960
BMI (kg/m2)	0.848	0.752	0.377
Family History of PC[a]	0.516	0.981	0.343
Alcohol Intake[b]	1.000	0.521	1.000
Smoking habit[c]	0.438	0.900	0.300

[a] Family history of PC in two categories: Yes; No.
[b] Alcohol intake in two categories: ≤1 drink/day (10grs of ethanol); >1 drink/day.
[c] Smoking habit in 3 categories: Never smoker, Former Smoker, Current Smoker.

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