Dietary Inflammatory Index and Prostate Cancer Risk: MCC-Spain study

Running title: Dietary Inflammatory Index and Prostate Cancer Risk

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Conflict of Interest: James R Hébert, own controlling interest in Connecting Health Innovations LLC, a company that has licensed the right to my invention of the DII®. Nitin Shivappa is an employee of Connecting Health Innovations LLC. The rest of authors declare that they have no conflict of interest.

ABSTRACT

Background: The etiology of prostate cancer (PCa) is not well-known, and the role of diet is not well established. We aimed to evaluate the role of the inflammatory power of the diet, measured by Dietary Inflammatory Index (DII®), on the risk of PCa.

Methodology: A population-based multicase-control (MCC-Spain) study was conducted. Information was collected on sociodemographic characteristics, personal and family antecedents, and lifestyles, including diet from a Food Frequency Questionnaire. The inflammatory potential of the diet was assessed using the energy-adjusted Dietary Inflammatory Index (E-DII) based on 30 parameters (a higher score indicates a higher inflammatory capacity of the diet). Tertiles of E-DII were created using the cut-off points from the control group. The International Society of Urology Pathology (ISUP) was grouped as ISUP 1, ISUP 2, or ISUP 3-5). Unconditional logistic regression models were used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the association between E-DII and PCa risk.

Results: A total of 928 PCa cases and 1278 population controls were included. Among PCa cases, the mean value of the E-DII score was 0.18 (SD: 1.9) vs. 0.07 (SD: 1.9) in the control group (p=0.162). Cases with a more pro-inflammatory diet (3rd tertile) had the highest risk of PCa, aOR_{T3vsT1}=1.30 (95% CI 1.03–1.65) (p-trend=0.026). When stratifying by ISUP, this risk association is only maintained for ISUP 2 and ISUP 3-5, aOR_{T3vsT1}=1.46 (95% CI 1.02–2.10) and 1.60 (95% CI 1.10–2.34), respectively

Conclusion: A positive association was observed between consuming a pro-inflammatory diet and PCa in the MCC-Spain population, specifically for an ISUP grade greater or equal than 2.

Keywords: dietary inflammatory index; prostate cancer; aggressiveness; case-control study; MCC-Spain.

1. Introduction

Prostate cancer (PCa) is the leading cancer in incidence among European men, and is the third leading cause of cancer death[1]. The incidence of PCa is widespread internationally, although with geographical differences, with Western countries being the most affected[2]. The effective primary prevention measures for PCa remains unknown, and therefore identifying potentially modifiable risk factors has become essential[3].

Diet has been postulated as a modifiable factor associated with PCa considering different approaches, namely at the level of isolated nutrients[4–6]; at the level of foods or food groups[5,7–10]; and as dietary patterns[11,12], but the evidence for many of these approaches is still scarce[13]. To date, the only dietary component considered by the International Agency for Research on Cancer (IARC) as a possible carcinogen agent (Group 2B) for this tumor is the consumption of red meat[14]. In comparison, the World Cancer Research Fund/American Institute for Cancer Research Third Expert Report classifies the consumption of dairy products, diet with high calcium intake, high concentrations of alpha-tocopherol and selenium as limited evidence for the PCa, not including other dietary factors[15].

Chronic low-grade systemic inflammation has been associated with a higher risk of chronic conditions such as cardiovascular disease and cancer[16,17]. Specifically, an inflammatory microenvironment may facilitate cellular proliferation in both benign and malignant prostatic conditions[18]. Dietary factors could influence this microenvironment, and a relationship has been shown between diet and blood levels of inflammatory markers such as C-reactive protein, TNF-α, IL-1, IL-2, and IFN-γ[19]. The Dietary Inflammatory Index (DII®) is a novel scoring system that estimates a diet's inflammatory potential from quantitative information.

To date, DII® has been associated with a higher risk of global cancer incidence and cancer mortality[20]. For specific sites, a positive association has been identified between a pro-inflammatory diet, evaluated through DII®, and increased risk of colorectal, and breast cancer[21,22]. A recent umbrella review of systematic review and meta-analyzes of observational studies determines there is no convincing evidence for the association between DII® and PCa risk[23]. The ethnic composition of the population, its dietary habits, and the number of dietary parameters used to build DII®, for example, could explain the differences found for PCa and other diseases. Moreover, PCa cannot be considered a unique pathology, and its behavior may be different depending on the degree of tumor aggressiveness. It is necessary to consider this factor in the analysis of the role of the pro-inflammatory diet and PCa.

Few studies have explored this association among European populations to date[24,25]. Therefore, we aimed to evaluate the association between the inflammatory potential of the diet, measured with the Dietary Inflammatory Index, and the risk of PCa, differentiating by the aggressiveness of the tumor in MCC-Spain.

2. Material and Methods

Design and study population

MCC-Spain is a population-based multicenter case-control study designed to identify risk and protective factors of the most common cancer sites (colorectal, breast, prostate, gastric tumors, and chronic lymphocytic leukemia) in adults. PCa participants and controls were enrolled from 7 Spanish provinces (Asturias, Barcelona, Cantabria, Granada, Huelva, Madrid, and Valencia) from 2008 to 2013. The study design and protocol have been described in detail elsewhere[26].

PCa cases were 40 to 85 years old and had a histologically confirmed newly diagnosed PCa (International Classification of Diseases 10th Revision (ICD-10): C61[27]). Simultaneously, a single set of population-based controls were frequency-matched to the overall distribution of cases, by 5-year intervals, age, sex, and study region using the primary care centers located in the hospitals' catchment areas. Of the total of 1112 PCa cases and 1493 controls recruited in MCC-Spain, after excluding participants without dietary data, those with implausible energy intake (with daily energy intakes lower than 800 kcal and higher than 4000 kcal[28]), and those with Gleason score under 6, 928 PCa cases and 1278 controls were included in the analyses (**Figure 1**).

Data collection

Face-to-face interviews were conducted by trained interviewers using a structured questionnaire. The information collected included sociodemographic data, lifestyle factors, environmental exposure, occupation and residential history, personal and family medical history (including a family history of prostate cancer), drug use, height, and weight. The information collection questionnaire can be consulted at https://www.mccspain.org/.

Diet was measured using a self-administered validated semi-quantitative Food Frequency Questionnaire (FFQ), which referred to the year before the interview. The FFQ used in this study was an adapted version of a Spanish-validated FFQ, which includes regional products[29]. It collected information on 140 food items across the different food groups, as well as the consumption of beverages. The FFQ included portion sizes and photos to assess doneness. Further, cross-check questions on food group intakes were included to adjust the frequency of food consumption and to reduce

misreporting of food groups with large numbers of items. Information about total energy intake and intake of both macronutrients and micronutrients, as well as alcohol consumption, were derived from Spanish food composition tables[30].

Dietary Inflammatory Index assessment

The energy-adjusted DII (E-DII) was calculated using a method previously developed by Shivappa et al. [31]. Briefly, the scoring algorithm, based on an extensive review of the literature from 1950 to 2010, focused on the effect of diet on six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and C-reactive protein). It contemplates 45 food parameters, including macronutrients, micronutrients, foods, and other dietary parameters. In the MCC-Spain study, we obtained information for 30 parameters[22,32], including anti-inflammatory parameters (fiber, monounsaturated fatty acid, polyunsaturated fatty acid, vitamins A, B1, B2, B3, B6, C, D, E, alcohol, folic acid, magnesium, zinc, anthocyanidins, flavan-3-ols, flavones, flavanols, flavanones, isoflavones, garlic, and onion) and pro-inflammatory parameters (carbohydrate, protein, total fat, cholesterol, saturated acid, vitamins B12 and iron).

For the construction of the E-DII the following steps were followed: i) the total amount consumed of each dietary parameter was standardized, subtracting the global daily mean intake and dividing by its standard deviation (SD) (data available on actual human consumption in 11 populations of different countries)[31]; ii) these values were rescaled to values from 0 to 1 point, with higher values indicating higher intakes (0 for minimum intake and 1 for maximum intake); iii) the value for each parameter was multiplied by 2, and then one point was subtracted, obtaining a score ranging from -1 to 1; iv) these values were multiplied by an overall food parameter-specific inflammation score (negative scores indicate anti-inflammatory capacity and positive scores indicate pro-inflammatory capacity)[31]; v) all the dietary parameter-specific were summed to create the overall DII® scores for each subject; and vi) E-DII scores were calculated by converting raw dietary components to amount per 1000 kcal. A lower E-DII score indicates a more anti-inflammatory diet, while a higher E-DII score represents a more pro-inflammatory diet. For more information about the estimation of DII®, Shivappa et al. may be consulted[31].

Clinical Information for PCa cases

The Gleason score and PSA at diagnosis were collected from the medical records of cases. The International Society of Urological Pathology (ISUP)[33] classification was established from the Gleason score: i) ISUP 1 (Gleason 3+3); ii)

ISUP 2 (Gleason 3+4); iii) ISUP 3 (Gleason 4+3); iv) ISUP 4 (Gleason 8); and v) ISUP 5 (Gleason >8). From this, three categories were defined : ISUP 1, ISUP 2, and ISUP 3-5.

Statistical analysis

The E-DII was analyzed as a continuous variable (per one-point increment) and as a categorical variable in tertiles built from the cut-points according to the control group's distribution. Characteristics were described using means and SD for continuous variables, and absolute and relative distribution for categorical variables in PCa cases and controls, and across E-DII tertiles in the control group. The first E-DII tertile (T1) was treated as the reference category (the lowest inflammatory diet). Logistic regression models with random province-specific intercepts were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to analyze the association between E-DII and PCa risk. Two logistic models were run: i) model 1, adjusting for age and educational level; and ii) model 2, additionally adjusting for family history of PCa, smoking status, body mass index (BMI), physical activity during leisure time from the age of 16 excluding the last year, and diabetes mellitus. The first model was adjusted only by variables derived from the design (age and educational level). Subsequently, the second model was executed based on prior knowledge and statistics criteria. Thus, in the latter, it was adjusted additionally by those variables that the scientific literature has related to PCa (family history of PCa, smoking status, body mass index, physical activity, and diabetes mellitus), and at the same time, we also included those variables that are related to the E-DII ($p<0.20$). Physical activity was categorized as follows: inactive (0 METs/week), low (0.1–8), moderate (8–15.9), and very active (≥16). Both models were also conducted stratifying by tumor aggressiveness. All statistical tests were two-sided and statistical significance was set at $p< 0.05$. Statistical analyses were performed using the statistical program Stata v.15 (Stata Corp., 2017, College Station, Tx, U.S.).

3. Results

The characteristics of PCa cases and controls are shown in **Table 1**. The E-DII score in the PCa group ranged from -5.02 (the highest anti-inflammatory score) to 5.63 (the highest pro-inflammatory score for cases) and from -4.96 to 5.47 in the control group. The mean E-DII score was slightly higher among PCa cases, 0.18 (SD: 1.9), than among controls 0.07 (SD: 1.9); the median was 0.03 among cases and -0.08 among controls. PCa cases compared to controls were slightly younger, with a lower educational level, a higher energy intake, and had a more frequent family history of PCa. Almost half of the cases (45.9%) had a PCa ISUP 1 tumor (Gleason score=6).

Table 2 shows the characteristics of PCa cases and controls across tertiles of E-DII. Compared to participants with a more anti-inflammatory diet (T1), those with a more pro-inflammatory diet (T3), for both cases and controls, were younger and with a lower education level (p=0.05). In addition, the participants in T3 had worse lifestyles compared to T1 participants: a higher percentage were current smokers, physically inactive, consumed a higher energy intake and alcohol.

The association between E-DII and overall PCa is shown in **Table 3**. Those participants with a more pro-inflammatory diet (T3) were observed to have a higher risk of developing PCa [aORT3vsT1= 1.30 (95% CI 1.03–1.65)] than those with the most anti-inflammatory diet (T1), with an indication of a dose-response relationship (p-trend=0.026).

Table 4 shows the association between E-DII and PCa according to ISUP classification. E-DII was associated with ISUP 2 and ISUP 3-5 tumors but not with tumors with an ISUP equal to 1. The positive association per each point of increase in E-DII and risk of PCa was observed only for ISUP 3-5 cases [aOR=1.12 (95% CI 1.03 – 1.22)]. This trend of risk was also observed using E-DII in tertiles: aORT3vsT1= 1.46 (95% CI 1.02 – 2.10) (p-trend=0.039) for ISUP 2 tumors, and aOR= 1.60 (95% CI 1.10 – 2.34) (p-trend=0.015) for ISUP 3-5 PCa cases.

4. Discussion

Our results indicate that consuming a pro-inflammatory diet, measured with the E-DII, was associated with an increased risk of PCa in the MCC-Spain population. Specifically, this association was observed for PCa cases with an ISUP greater or equal than 2 (Gleason score≥7).

Taking into account that the diet could modulate chronic inflammation, which has been postulated as a possible cancer risk factor and could play a key role in the development of PCa[34], it is important to identify factors related to an inflammatory status, such as the diet. The DII® allows a global approximation of the inflammatory influence of a diet, as nutrients and foods are consumed in combination, producing synergistic effects between them. Our results suggest the existence of a dose-response association between E-DII and overall PCa risk. These findings agree with previous studies[24,25,35–40]. On the other hand, three studies, a US case-control study, a Mexican case-control study, and a US cohort study, did not find a relationship between a DII® and PCa[41–43]. The study of Vidal et al. and the study of Vázquez-Salas et al.[41,43] suggest an association between PCa and DII®, although they do not reach statistical significance, perhaps because the sample size was not very large (328 controls and 254 PCa cases and 794 controls and 394 PCa cases, respectively). In the same way, the cohort study of McMahon et al.[42] found an association only

between a pro-inflammatory diet and the risk of PCa for white men. As McMahon et al. say, "*the differences in time-to-prostate-cancer diagnosis observed between quartiles within each race stratum may have been due to the arbitrary selection of cut-off points in that analysis."* This is a common problem for this type of study. The characteristics of the dietary pattern for each population may condition the observed association. The participants´ diet quality may be moderate-high in general, and therefore detecting an association is difficult.

Despite different papers present in literature exploring the relationship between pro-inflammatory diet and PCa risk, a high heterogeneity among studies has been observed [24,25,35–43]. This could be due to: i) the defined exposure cut-off points were derived from their own populations, as described previously; ii) the diet was collected by FFQ, and were self-administered in the majority of the studies, whereas in others, it was collected through an interviewer[25,35,36] or a telephone call[24]; iii) the dietary collection was performed from the time of biopsy months to 5 years after diagnosis for case-control studies[25,35–39,41,43]; or iv) diverse populations, including Vietnam[35], Argentina[36], Iran[38,39]. The Spanish population's typical dietary pattern is a Mediterranean dietary pattern characterized by its anti-inflammatory power[44]. However, despite working with this Mediterranean population, our results still detected an inverse relationship between the anti-inflammatory capacity of a diet and the risk of PCa.

When stratified by aggressiveness, the highest risk association between E-DII and PCa was for the ISUP 3-5 tumors, followed by ISUP 2. Most previous studies have analyzed the association between DII and PCa, without considering tumor aggressiveness[24,25,36–40]. Those studies exploring tumor aggressiveness suggest a higher risk for high aggressiveness PCa cases[41–43]. Hoang et al. did not find differences between low-moderate and high-grade PCa cases[35]; however, all cases with a Gleason score equal 7 were considered as low-moderate grade, against ISUP recommendations[33]. That high aggressiveness cases have a higher risk would be in line with a previous study suggesting that an inflammatory microenvironment promotes PCa progression and creates a continuous loop that stimulates a more aggressive stage[45]. Hence, consuming a diet rich in anti-inflammatory parameters such as vitamins, garlic, or onion and with little content of pro-inflammatory parameters such as cholesterol, total fat, or iron, could modulate PCa risk of moderate and high aggressiveness.

Some limitations should be considered when interpreting our results. Although we used the E-DII, a widely accepted method, direct comparison with the results of previous studies is problematic for several reasons: i) the number of parameters included in the DII® varies between studies, from the 21 to 36 food parameters; ii) some studies assessed

the inflammatory potential of the diet using the DII® and not E-DII. However, the E-DII has been the method that has been used in the most recent publications as it considers energy as a step for the construction of the final score; and iii) the categorization of E-DII has been made according to the tertiles for the control group, and therefore, they are population-dependent cut-off points. Finally, inflammatory biomarkers are not available in the MCC-Spain study, and therefore it was not possible to correlate the E-DII score with these biomarkers. Despite that, the construct validity of DII®/E-DII compared to a variety of inflammation biomarkers has been established in previous studies[46,47].

Regarding the strengths of our study, the following should be highlighted: i) to our knowledge, this is the first study investigating the association between the E-DII and PCa risk according to tumor aggressiveness of PCa in a European population; ii) the E-DII has been used widely for different health outcomes[22,32,48], and has good validity that has been demonstrated in previous studies[46,47]; iii) this study is based on a relatively large sample, allowing analysis stratified by aggressiveness; iv) we have used the ISUP grade grouping to measure the aggressiveness, a categorization recommended by the ISUP in the last Consensus Conference on Gleason Grading of Prostatic Carcinoma[33]; and v) to minimize recall bias, we use a validated questionnaire for dietary information collection, which includes regional products[29]. We consider that if there were recall bias, it would have affected cases and controls in the same way, thus being a non-differential bias. Moreover, although the FFQ refers to the previous year, dietary habits have been shown to remain fairly stable over time[49].

As conclusions, an association was observed between a pro-inflammatory diet and PCa risk in a Spanish population. This positive association was stronger in PCa cases of moderate and high aggressiveness. Future studies are needed to understand the role of diet in determining the extent and aggressiveness of PCa, which would impact clinical and public health recommendations.

Conflict of Interest: James R Hébert, own controlling interest in Connecting Health Innovations LLC, a company that has licensed the right to my invention of the DII®. Nitin Shivappa is an employee of Connecting Health Innovations LLC. The rest of authors declare that they have no conflict of interest.

Ethics approval and consent to participate: All participants who were eligible to participate in the study and agreed to participate were fully informed about the study objectives and signed an informed consent form. The study was approved by the Ethics Committee of all participating centers, in conformity to the principles of the Declaration of Helsinki.

Availability of Data and Materials: The data that are used in this study are available from the corresponding author upon reasonable request.

Author Contributions: GC-V, MP, MK and JJJ-M conceptualisation and design of the study; ML-L, IS-B, RO-R, GC-V, NS, JRH and JJJ-M formal analysis of data; GC-V, PA, BP-G, JA, GF-T, NA, MP, MK and JJJ-M funding acquisition; GC-V, NA, MP and MK project administration; ML-L, and JJJ-M first draft of this paper. All authors contributed to the interpretation of the results and revised the manuscript.

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Figure Legends

Figure 1: Flow-chart of prostate cancer (PCa) cases and controls selection.

Figure 1: Flow-chart of prostate cancer (PCa) cases and controls selection.

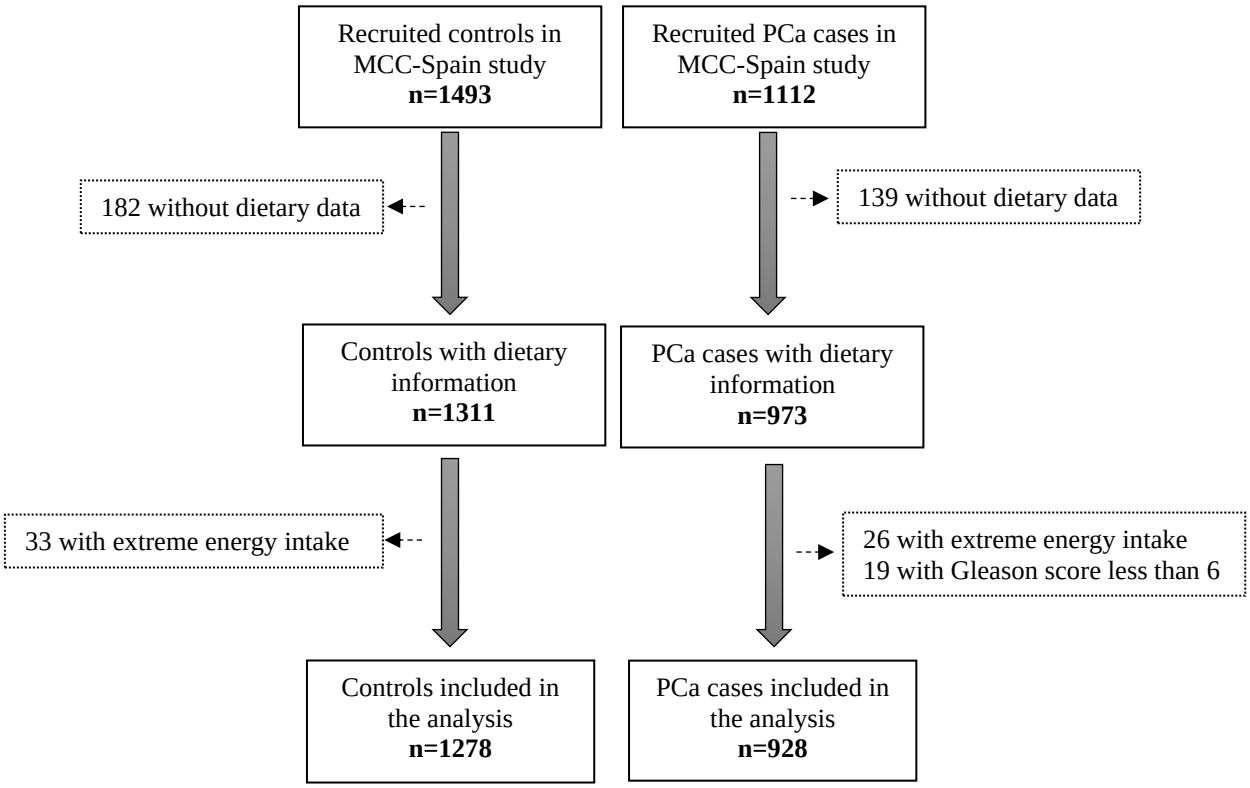

Table 1. Characteristics of prostate cancer (PCa) cases and controls in MCC-Spain study.

	Controls n=1278	PCa cases n=928	p-value
E-DII score, mean (SD) (min; max)	0.07 (1.9) (-4.96; 5.47)	0.18 (1.9) (-5.02; 5.63)	0.162
Age (years), mean (SD)	66.4 (8.6)	65.9 (7.3)	0.141
Age (years), n (%)			<0.001
40 to 54	113 (8.8)	58 (6.32)	
55 to 69	672 (52.6)	574 (61.9)	
70 to 80	493 (38.6)	296 (31.9)	
Education level, n (%)			<0.001
Less than primary/Primary	650 (50.9)	581 (62.6)	
Secondary	353 (27.6)	204 (22.0)	
University	278 (21.5)	143 (15.4)	
BMI (kg/m^2), mean (SD)	27.4 (3.7)	27.5 (3.5)	0.610
BMI (kg/m^2), n (%)			0.846
<25	311 (24.3)	220 (23.7)	
≥25 to <30	672 (53.6)	503 (54.2)	
≥30	266 (20.8)	191 (20.6)	
Missing	29 (2.3)	14 (1.5)	
Smoking status, n (%)			0.203
Never	344 (26.9)	278 (30.0)	
Former	661 (51.7)	447 (48.2)	
Current	270 (21.2)	201 (21.6)	
Missing	3 (0.2)	2 (0.2)	
Physical activity[1], n (%)			0.450
Inactive	329 (25.7)	246 (26.5)	
Low	466 (36.5)	322 (34.7)	
Moderate	209 (16.4)	148 (16.0)	
Very active	255 (19.9)	212 (22.8)	
Missing	19 (1.5)	-	
Family history of PCa, n (%)			<0.001
No	1178 (92.2)	733 (79.0)	
Yes	97 (7.6)	192 (20.7)	
Missing	3 (0.2)	3 (0.3)	
Diabetes Mellitus, n (%)			0.069
Yes	215 (16.8)	134 (14.4)	
No	1008 (78.9)	781 (84.2)	
Missing	55 (4.3)	13 (1.4)	
Energy intake (kcal/day), mean (SD)	2005.7 (583.1)	2063.6 (593.1)	0.022
Alcohol intake (g/day), mean (SD)	17.3 (19.6)	17.3 (19.8)	0.995
ISUP grade, n (%)			
1	-	422 (45.5)	
2	-	277 (29.8)	
3	-	97 (10.5)	
4	-	70 (7.5)	
5	-	54 (5.8)	
Missing	-	8 (0.9)	
PSA levels at diagnosis, mean (SD)	-	13.3 (49.6)	

BMI: Body Mass Index; E-DII: dietary inflammatory index adjusted by energy; ISUP: International Society of Urological Pathology; SD: standard deviation. [1]Leisure physical activity, from the age of 16 excluding the last year, measured METs/week: inactive (0), low (0.1–8), moderate (8–15.9), and very active (≥16). Note: missing data are not included for comparing cases and controls.

Table 2. Characteristics of prostate cancer (PCa) cases and controls according to tertiles (T1, T2, and T3) of E-DII score.

	Controls				PCa cases			
	E-DII tertiles cut-points*				E-DII tertiles cut-points*			
	T1 n=426	T2 n=426	T3 n=426	p-value	T1 n=282	T2 n=306	T3 n=340	p-value
Age (years), mean (SD)	67.9 (7.7)	67.2 (8.2)	64.2 (9.4)	<0.001	68.0 (6.3)	65.6 (7.2)	64.6 (7.8)	<0.001
Age (years), n (%)				<0.001				<0.001
40 to 54	19 (4.4)	27 (6.3)	67 (15.7)		3 (1.0)	20 (6.5)	35 (10.3)	
55 to 69	224 (52.6)	223 (52.4)	225 (52.8)		166 (58.9)	194 (63.4)	214 (62.9)	
70 to 80	183 (43.0)	176 (41.3)	134 (31.5)		113 (40.1)	92 (30.1)	91 (26.8)	
Education level, n (%)				0.004				0.026
Less than primary/Primary	227 (53.3)	227 (53.3)	196 (46.0)		196 (69.5)	179 (58.5)	206 (60.6)	
Secondary	198 (23.0)	109 (25.6)	146 (34.3)		45 (16.0)	74 (24.2)	85 (25.0)	
University	101 (23.7)	90 (21.1)	84 (19.7)		41 (14.5)	53 (17.3)	49 (14.4)	
BMI (kg/m^2), mean (SD)	27.5 (3.7)	27.4 (3.9)	27.4 (3.4)	0.832	27.6 (3.7)	27.5 (3.2)	27.64 (3.5)	0.636
BMI (kg/m^2), n (%)				0.229				0.402
<25	93 (21.8)	115 (27.0)	103 (24.2)		73 (25.9)	65 (21.2)	82 (24.1)	
≥25 to <30	241 (56.6)	221 (51.9)	210 (49.3)		141 (50.0)	178 (58.2)	184 (54.1)	
≥30	86 (20.2)	83 (19.5)	97 (22.8)		64 (22.7)	60 (19.6)	67 (19.7)	
Missing	6 (1.4)	7 (1.6)	16 (3.7)		4 (1.4)	3 (1.0)	7 (2.1)	
Smoking status, n (%)				<0.001				<0.001
Never	125 (29.3)	122 (28.6)	97 (22.8)		99 (35.1)	92 (30.1)	87 (25.6)	
Former	246 (57.7)	220 (51.7)	195 (45.8)		138 (48.9)	153 (50.0)	156 (45.9)	
Current	53 (12.5)	84 (19.7)	133 (31.2)		44 (15.6)	60 (19.6)	97 (28.5)	
Missing	2 (0.5)	-	1 (0.2)		1 (0.4)	1 (0.3)	-	
Physical activity[1], n (%)				0.009				0.138
Inactive	83 (19.4)	117 (27.5)	129 (30.3)		63 (22.3)	88 (28.8)	95 (27.9)	
Low	178 (41.8)	151 (35.4)	137 (32.1)		102 (36.2)	115 (37.6)	105 (30.9)	
Moderate	75 (17.6)	70 (16.4)	64 (15.0)		53 (18.8)	42 (13.7)	53 (15.6)	
Very active	85 (20.0)	82 (19.3)	88 (20.7)		64 (22.7)	61 (19.9)	87 (25.6)	
Missing	5 (1.2)	6 (1.4)	8 (1.9)		-	-	-	
Family history of PCa, n (%)				0.856				0.194

No	390 (91.5)	396 (93.0)	392 (92.0)		228 (80.9)	232 (75.8)	273 (80.3)	
Yes	34 (8.0)	30 (7.0)	33 (7.8)		53 (18.8)	74 (24.2)	65 (19.1)	
Missing	2 (0.5)	-	1 (0.2)		1 (0.3)	-	2 (0.6)	
Diabetes Mellitus, n (%)				0.074				0.113
Yes	82 (19.3)	74 (17.4)	59 (13.9)		50 (17.7)	42 (13.7)	42 (12.4)	
No	323 (75.8)	331 (77.7)	354 (83.1)		224 (79.4)	260 (85.0)	297 (87.43)	
Missing	21 (4.9)	21 (4.9)	13 (3.0)		8 (2.9)	4 (1.3)	1 (0.3)	
Energy intake (kcal/day), mean (SD)	1871.2 (539.6)	1990.5 (589.3)	2155.4 (585.1)	<0.001	1937.0 (562.0)	2029.1 (578.9)	2199.6 (604.6)	<0.001
Alcohol intake (g/day), mean (SD)	14.8 (15.4)	16.1 (18.6)	21.2 (23.4)	<0.001	14.2 (14.0)	16.6 (19.4)	720.6 (23.4)	<0.001
ISUP grade, n (%)				-				0.387
1	-	-	-		136 (48.2)	148 (48.4)	138 (40.6)	
2	-	-	-		73 (25.9)	90 (29.4)	114 (33.5)	
3	-	-	-		29 (10.3)	31 (10.1)	37 (10.9)	
4	-	-	-		24 (8.5)	21 (6.9)	25 (7.3)	
5	-	-	-		18 (6.4)	13 (4.2)	23 (6.8)	
Missing	-	-	-		2 (0.7)	3 (1.0)	3 (0.9)	
PSA levels at diagnosis, mean (SD)	-	-	-		15.2 (70.3)	9.2 (8.7)	15.4 (50.5)	0.213

BMI, Body Mass Index; E-DII: dietary inflammatory index adjusted by energy; ISUP: International Society of Urological Pathology; SD, standard deviation.

*E-DII tertiles cut-points: T1: ≥-4.96 to <-0.94; T2: ≥-0.94 to <0.87; and T3: ≥0.87 to <5.47

[1]Leisure physical activity, from the age of 16 excluding the last year, measured METs/week: inactive (0), low (0.1–8), moderate (8–15.9), and very active (≥16). Note: missing data are not included for comparisons.

Table 3. Association between E-DII and overall prostate cancer (PCa).

1-Point increase of E-DII			**E-DII tertiles cut-points**			
			T1: ≤-0.95	**T2: >-0.95 to ≤0.87**	**T3: >0.87**	
Cases (n)			282	306	340	
	aOR (95% CI)	***p-value***		aOR (95% CI)	aOR (95% CI)	**p-trend**
Model 1	1.03 (0.99-1.08)	0.117	1.00 (ref.)	1.08 (0.87–1.34)	1.24 (1.00–1.55)	0.049
Model 2	1.05 (0.99-1.10)	0.082	1.00 (ref.)	1.09 (0.87–1.37)	1.30 (1.03–1.65)	0.026

E-DII: dietary inflammatory index adjusted by energy.
Model 1: adjusted for age and educational level.
Model 2: adjusted for age, educational level, family history of PCa, smoking status, body mass index, physical activity and diabetes mellitus.

Table 4. Association between E-DII and prostate cancer (PCa) cases according to International Society of Urological Pathology (ISUP) classification.

	1-Point increase of E-DII aOR (95% CI)	***p-value***	**E-DII tertiles cut-points** **T1: ≤-0.95** aOR (95% CI)	**T2: >-0.95 to ≤0.87** aOR (95% CI)	**T3: >0.87** aOR (95% CI)	**p-trend**
ISUP 1						
Cases (n)			136	148	138	
Model 1	0.99 (0.93–1.05)	0.830	1.00	1.04 (0.79–1.37)	1.00 (0.75–1.33)	0.984
Model 2	1.00 (0.93–1.07)	0.990	1.00	1.07 (0.80–1.43)	1.06 (0.78–1.43)	0.719
ISUP 2						
Cases (n)			73	90	114	
Model 1	1.06 (0.98–1.14)	0.096	1.00	1.20 (0.85–1.70)	1.51 (1.07–2.13)	0.016
Model 2	1.05 (0.97–1.14)	0.201	1.00	1.20 (0.84–1.73)	1.46 (1.02–2.10)	0.039
ISUP 3–5						
Cases (n)			71	65	85	
Model 1	1.08 (1.00–1.17)	0.041	1.00	0.94 (0.65–1.36)	1.40 (0.98–2.01)	0.062
Model 2	1.12 (1.03–1.22)	0.009	1.00	1.00 (0.68–1.47)	1.60 (1.10–2.34)	0.015

E-DII: dietary inflammatory index adjusted by energy; ISUP: International Society of Urological Pathology.
Model 1: adjusted for age, and educational level.
Model 2: adjusted for age, educational level, family history of PCa, smoking status, body mass index, physical activity, and diabetes mellitus.