HIGH ADHERENCE TO WESTERN DIETARY PATTERN AND PROSTATE CANCER RISK: FINDINGS FROM THE EPIC-SPAIN COHORT

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High adherence to Western dietary pattern and prostate cancer risk: findings from the EPIC-Spain cohort

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ABSTRACT:

Objective: To explore the association between three previously identified dietary patterns (Western, Prudent and Mediterranean) and prostate cancer risk by tumour aggressiveness.

Subjects and methods: The Spanish cohort of the European Prospective Investigation into Cancer and Nutrition study provided dietary and epidemiological information from 15,296 men recruited during 1992-1996. The associations between the adherence to the three dietary patterns and prostate cancer risk (global, for Gleason grade groups =6 and >6 and for ISUP 1+2 ; ISUP 3+4+5) was explored with multivariable Cox proportional hazards regression models stratified by centre and age.

Results: While no effect over prostate cancer risk was detected for the Prudent and Mediterranean dietary patterns, a suggestive detrimental effect of the Western dietary pattern was found (HR_{Q4vsQ1} (95% CI): 1.29 (0.96;1.72)). This effect was only observed for Gleason grade group >6 (HR_{Q3vsQ1}(95%CI) =1.61(1.00; 2.59) and HR_{Q4vsQ1}(95%CI) = 1.60 (0.96; 2.67)) and specially ISUP 3+4+5 tumours ((HR_{Q2vsQ1}(95%CI) =1.97 (0.98; 3.93); HR_{Q3vsQ1}(95%CI) =2.72(1.35; 5.51) and HR_{Q4vsQ1}(95%CI) = 2.29 (1.07; 4.92)).

Conclusions: Our results suggest that a high adherence to a healthy-type diet such as the represented by the Prudent and Mediterranean dietary patterns is not enough to prevent PC. Additionally, reducing the adherence to a Western-type diet seems to be necessary.

Keywords: Dietary patterns; Diet, Mediterranean; Prostate Neoplasms; Cancer; EPIC-Spain.

Abbreviations:

95%CI: 95% confidence interval.

EPIC: European Prospective Investigation into Cancer and Nutrition.

HR: Hazard Ratio.

IQR: Interquartile Range.

PC: Prostate Cancer.

Introduction

According to the last global cancer statistics estimates, in 2020, prostate cancer (PC) was the fourth most diagnosed cancer globally and the second among males worldwide [1]. However, its aetiology is mostly unknown. While the evidence of a possible effect of race, age and family history of PC in the incidence of this tumour is strong, the role of other modifiable risk factors such as body composition, physical activity, smoking, alcohol or diet is unclear [2]. According to the last Word Cancer Research Fund and American Institute for Cancer Research report on diet, nutrition physical activity and PC from 2018, it is probable that a high adult attained weight and a high body fatness increase the risk of PC and limited but suggestive evidence relates this tumour with a high consumption of products rich in calcium and to low concentrations of alpha tocopherol and selenium in plasma [3].

The lack of conclusive evidence about the association between diet and cancer might be partly explained by the fact that most studies explore the effect of individual foods and nutrients in PC risk even though foods and nutrients are not consumed individually. Dietary patterns may better reflect the variability and food interactions in the population's diet [4]. A *priori* and a *posteri* dietary patterns are frequently used to explore the association between diet and disease. The latter are identified using the dietary information of the sample under study, ensuring their independence from disease and the representativeness of the individuals' diet. However, few studies have explored the association between *a posteriori* dietary patterns and PC risk [5–19] and the existing evidence is still inconclusive.

A previous case-control study carried out in Spain, identified three dietary patterns (Western, Prudent and Mediterranean) that characterize the diet of the Spanish women and showed some associations with breast cancer risk [20]. After checking the applicability [21] of these patterns, they were applied in a different multicase case-control study (MCC-Spain) showing different associations with other tumours, including PC [7]. Results indicated a potential protective effect of high adherences to the Mediterranean dietary pattern over aggressive PC tumours.

The objective of the present study is to externally validate the previous results [7] and to provide more evidence regarding the association of *"a posteriori"* dietary patterns and PC risk by applying the three dietary patterns over the European Prospective Investigation into Cancer and Nutrition Spanish cohort data (EPIC-Spain).

Subjects and methods

Study population

EPIC is a multicentric and prospective cohort study designed to investigate the relationship between environmental factors, lifestyle, diet, and cancer. We used data from the Spanish cohort (EPIC-Spain), that recruited between 1992 and 1996, information of 41437 healthy adults aged 29–69 years from five Spanish regions in the north (Asturias, Guipuzkoa and Navarra) and south, including the Mediterranean shore (Granada and Murcia), of Spain from which 15 296 men were selected [22].

Information about physical activity, alcohol, smoking, educational level and medical history of previous illnesses was collected in a personal interview using a questionnaire. Individual dietary information during the year before enrolment was collected using a computerized dietary history questionnaire, previously validated in Spain and administered by trained interviewers. Anthropometric measurements were taken by trained personnel using standardised procedures [22].

The ethical review boards from the International Agency for Research on Cancer (IARC) and the Medical Ethics Committee of the Bellvitge Hospital (Barcelona) approved the study, and all the eligible participants gave their informed consent.

Case ascertainment and follow-up period

Cases were identified by linking the EPIC-Spain data with the population-based cancer registries of the five mentioned regions and were defined as first occurrence of a primary malignant PC (C619 of the ICD-10). Dates and causes of death were extracted from the population-based mortality registries of the National Institute of Statistics. Additionally, clinical reports were reviewed to classify PC aggressiveness into Gleason grade groups =6 vs >6 and also considering the International Society of Urological Pathology (ISUP) grading [23].

The follow up period was defined as the time from the date of recruitment to the date of diagnosis of any type of malignant tumour, death or last completed follow-up date depending on which occurred first. Censoring dates for the last complete follow-up were 31st of December 2012 for Granada, 31st of December 2013 for Murcia, 31st of December 2011 for Navarra, 30th of December 2013 for Guipuzkoa and 31st of December 2010 for Asturias.

Food groups and component loadings

Three dietary patterns were identified in the controls sample of the Spanish multicentric case-control study on female breast cancer EpiGEICAM [20] that have been associated with different tumour locations, including PC [7]: 1) Western dietary pattern, consisting in high consumption of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, convenience food and sauces and low intake of low-fat dairy products and whole grains; b) Prudent dietary pattern characterized by high intakes of low-fat dairy products, vegetables, fruits, whole grains and juices; and c) Mediterranean dietary pattern representing high intakes of fish, vegetables, legumes, boiled potatoes, fruits, olives and vegetable oil, and a low intake of juices. In the original sample the three patterns explained 16%, 13% and 8% of total variability of food intake respectively.

These patterns were identified by applying principal components analysis (PCA) without rotation of the variance-covariance matrix over 26 food groups, resulting in a matrix of weights (pattern loadings) that can be used to apply such patterns in other samples as explained in detail elsewhere [21]. For the case of the EPIC-Spain participants, their adherence to the Western, Prudent and Mediterranean dietary patterns was calculated grouping the food items derived from the dietary history questionnaire (excluding non-caloric and alcoholic beverages) into the same 26 food groups defined in the EpiGEICAM study. Since alcohol intake is an already established risk factor for breast cancer, it was considered more appropriated to include it in the analysis as a possible confounder than considering it as an independent group in the PCA analysis. For some dairy and fish products whose type was not specified, a weighted distribution was done based on the 1998 food consumption data from the Spanish Ministry of Agriculture, Food and Environment (MAPAMA)[24] taking also into account the distribution of these foods among cancer and non-cancer cases observed in MCC-Spain [7] (**Table S1**). Subsequently, the scores of adherence to the Western, Prudent and Mediterranean dietary patterns were calculated as a linear combination of the EpiGEICAM [20] pattern loadings and the food group consumption reported in the EPIC-Spain study. The adherence to these three dietary patterns was modelled as a categorical variable (quartiles of adherence) and as a continuous variable (one standard deviation increment in the score). We used the quartiles of the distribution for the whole EPIC sample to ensure comparability of our results with the MCC-Spain study (that also used non-sex specific cut points) and among different tumours within the EPIC study.

Statistical analyses

Crude and adjusted associations between the adherence to each of the three dietary patterns and PC risk (global and by tumour aggressiveness) were explored by fitting centre and age (5-years intervals from 30 to 70 years old) stratified multivariable Cox proportional hazards regression models that assume the same HR for all strata but different baseline non-parametric hazards for all combinations of the values of the stratifying variables, relaxing the PH assumptions for such variables. These models were adjusted by total energy intake, body mass index (BMI), height, and educational level at recruitment. For the Western dietary pattern, models were also adjusted by the adherence to the Prudent and Mediterranean dietary patterns and for the Prudent and Mediterranean dietary patterns models were also adjusted by the adherence to the Western dietary pattern. Additional adjustment by physical activity (occupational and recreational), lifetime alcohol intake and smoking habit did not meaningfully changed the associations. To eliminate possible prevalent cases undiagnosed at the time of recruitment, the first-year follow-up was discarded. The p-value for linear trend was calculated by including the categorical variable as continuous in the models and testing if the resulting slope was significantly different from zero. Finally, nonlinear associations were modelled through restricted cubic splines with knots at the 5^{th}, 35^{th}, 65^{th} and 95^{th} percentiles. The p-value for curvature of splines was calculated by simultaneously testing whether the coefficients of the non-linear terms in the model were significantly different from zero.

In all cases, the fulfilment of the proportional hazards assumption was checked visually with standardized survival curves by quartiles of adherence to the each pattern (**Figure 1 and supplementary material figures S1-S3**) and numerically by testing the nonzero slope in a generalized linear regression of the scaled Schoenfeld residuals on time. Smooth estimates of the standardized survival curves for prostate cancer by quartile of each dietary pattern were obtained using spline-based survival models [25]. These models parameterized the baseline log cumulative hazard as a natural cubic spline of log time with three internal knots at the 25th, 50th, and 75th percentiles of the uncensored log time distribution and assumed proportional hazards over time across dietary quintiles. The resulting survival curves for each quartile of dietary pattern were standardized to the distribution of baseline confounders in the overall study population. Analyses were performed using the stpm2 and standsurv commands in Stata. The violation of the assumption of proportional hazards observed in some cases due to lack of proportionality for age estimates, was solved with the already mentioned adjustment of age-stratified cox models.

All analyses were performed using Stata/MP version 17 (Statacorp, College Station, TX).

Results

After excluding 181 men for implausible energy intakes under 750 or above 4,500 kcals per day, 3 with a BMI over 60, 72 males with non-clinically relevant PC (Gleason grade ≤5), and the first year follow up (77 individuals with censor date in the first year of follow up), the sample size was of 15296 individuals. Among them, 609 PC cases were identified during a median follow-up of 16.99 years. Additionally, 165 individuals for the full sample and 319 for the Gleason grade group adjusted analyses were excluded due to missing values in some of the variables included in the models (**Figure 1**).

Men in the second to fourth quartiles of adherence to the Western dietary pattern showed higher alcohol intake than those in the first quartile and those in the fourth quartile of adherence to the Western dietary pattern showed higher energy intake, higher prevalence of current smokers, lower age and lower percentage of higher education. Despite of being significant, no remarkable differences were observed in the distribution of BMI and physical activity across quartiles of adherence to the Western Pattern. High adherences to the Prudent dietary pattern were associated with lower alcohol intake, BMI, age at recruitment and physical activity and with higher proportion of non-smokers, energy intake and education level. Finally, participants with the highest adherences to the Mediterranean diet presented higher alcohol and energy intake, slightly lower BMI and age, were more active, slightly more educated and smoked less (**Table 1**).

While no association of PC risk was found with a high adherence to the Prudent dietary pattern, results indicated a suggestive increase in PC risk with growing adherences to the Western dietary pattern (HR_{Q4vsQ1} (95% CI):1.29 (0.96;1.72)) (**Table 2**) that seemed to be confined to aggressive tumours (Gleason grade group >6) (HR_{Q3vsQ1} (95% CI):1.61 (1.00;2.59) HR_{Q4vsQ1} (95% CI):1.60 (0.96;2.67)) and specially for tumours in the categories 3, 4 and 5 of the ISUP classification (HR_{Q2vsQ1} (95% CI):1.97 (0.98;3.93); HR_{Q3vsQ1} (95% CI):2.72 (1.35; 5.51) and HR_{Q4vsQ1} (95% CI):2.29 (1.07;4.92)) for adherences as low as those in the second quartile (**Table 3**). The suggestive positive linear trend observed for the association of the Mediterranean dietary pattern with aggressive tumours (Gleason grade group >6 and ISUP 3+4+5), was not confirmed by the analyses by quartiles.

The exploration of non-linear associations did not reveal remarkable departures from linearity, except for the case of the Prudent dietary pattern that showed a suggestive U-shape association with ISUP grades 1 and 2 PC but with HR that did not achieve statistical significance (**Supplementary material, Figures S3-S5**).

Discussion

Our results indicate that, while high adherences to widely considered healthy patterns such as the Prudent and Mediterranean seem to have no effect in PC risk, a moderate to high adherence to the Western dietary pattern might have a considerable detrimental effect for aggressive PC risk (Gleason grade group >6 and ISUP grades 3-5).

As for the validation of the previous results, MCC-Spain [7] did not report a relationship between a high adherence to the Western dietary pattern and PC risk, but the direction of associations are concordant with our results. Also, we did not detect the strong protective effect of the Mediterranean pattern for aggressive PC tumours reported in MCC-Spain. Differences in the dietary habits of the subjects from both studies might be behind these discrepancies. High consumption of products rich in calcium and low plasma concentrations of alpha tocopherol (present mainly in wheat germ and sunflower oils) and selenium (found principally animal foods) have been associated to PC risk [3]. Also, skimmed dairy intake is related to lower vitD plasma levels [26] which can result in poorer calcium absorption that is associated with increased PC risk [3]. EPIC-Spain participants showed higher intake of high-fat dairy (+76grs/day), red (+36grs/day) and processed (+14grs/day) meat, total animal foods (+93grs/day) and refined grains (+71grs/day) and lower consumption low-fat dietary products (-162grs/day). Additionally, data form the MAPAMA [24] reveal a significant decrease in sunflower oil intake during the last years (EPIC collected information from 1992-1996 and MCC-Spain form 2008-2013). Therefore, the greater intake of products with high content in nutrients associated to increased PC risk in the EPIC-Spain sample might be potentiating the effect of the Western dietary pattern and counteracting the beneficial effect of Mediterranean pattern, partly justifying the mentioned discrepancies with the MCC-Spain results.

Our conclusions agree with the still scarce published evidence. Most studies exploring the association between *a posteriori* dietary patterns and PC risk identify one or various healthy-type patterns, usually labelled as Mediterranean/Healthy/Prudent, with heterogeneous compositions [5–19]. Some of them represent a high consumption of fruits, vegetables and whole grains [9,11–14,16,19] (similar to our Prudent pattern) and others additionally include legumes, nuts, olive oil, fish and/or poultry [5–8,10,14–18] (agreeing with our Mediterranean pattern) but only few of them find a protective effect of this type of diet against PC [5–7,10]. The identification of a Western-type dietary pattern with a more uniform composition (high consumption of meat, sweets, convenience food, sauces and snacks) [5–19] related to increased PC risk [5,6,8–11,13,16–18] is also common. It seems that the evidence is still insufficient to claim a preventive effect of a Mediterranean-type healthy diet and, despite the fact that the agreement about the detrimental effect of the Western diet over PC risk is bigger, it should be not forgotten that the number of cohort studies published is still small [14,17,19] and that further investigations are necessary to support these findings.

The high intake of dairy products characteristic of our Western pattern, is known to increase the risk of PC [3] by suppressing the formation of 1,25-dihydroxyvitamin D (with antitumor effect on human prostatic cells in vitro [27]) and by raising the circulating levels of IGF-I [28] which stimulates proliferation and inhibits apoptosis in PC cells [29]. Also, total and saturated fats and trans fatty acids from red and processed meats, sweets, sauces and convenience food, are suspicious of enhancing PC progression through the disruption of prostate hormonal regulation (which favours androgen receptor stimulation) and increasing oxidative stress (that impairs the repair of DNA damage) and inflammation (that increases cellular proliferation) [28]. Also, many compounds that are naturally present (heme iron) or generated when cooking or processing red meat or other products (nitrites, benzo[a]pyrene and heterocyclic and polycyclic aromatic amines) might act over PC risk by catalysing free radical formation and suppressing the expression of genes involved in cell cycle progression and DNA repair in PC cells [28]. Finally, the highly energetic profile of the Western diet contributes to increase body composition, the most important known modifiable risk factor for PC [7].

The differential effect of the Western diet over PC by tumour aggressiveness has also been explored in other studies [5–7,14,16,17] and all of them found an increased effect of diet in PC risk among aggressive tumours, three of them specifically for the Western diet [5,16,17]. In Spain, the screening program for PC implemented in 1994 might be behind this differential effect. This program detects many low-grade indolent tumours with no clinical relevance that would otherwise remain undiagnosed. The clinical characteristics and the risk profiles of men presenting these low-grade indolent tumours might be different from those presenting high-grade tumours.

Our study has some limitations, being one of the most important the impossibility to ensure that diet has not changed over time. However, a recent study points out that the eating patterns of the Spanish population have changed significantly over the last 40 years, moving away from the Mediterranean diet in favour of a more westernised pattern [30]. Therefore, if different, the effect of the Western dietary pattern on PC risk will likely be even higher than the suggested by our results. Additionally, information about family history of PC or race, two important risk factors for PC, was not collected. However, family history of PC is not likely to modify dietary habits, as the sensitivity analysis we carried out with tumours that recorded this information (breast and colorectal) indicated (data not shown). Including family history in the models for breast and colorectal cancer barely changed the associations with the three dietary patterns (+/- 0.02 changes in the HR). With regard to race, black men are known to have higher risk of PC and might present different dietary habits. We do not have concrete data on the black population in Spain, but we do not expect it to be large, especially at the time the data were collected (1992-1996). Most of the black Spanish population is immigrated. Taking into account that immigrated population in 1995 was around 2.56% and that this population is less likely to be contacted, it is not unreasonable to think its representation in EPIC-Spain cohort is significantly lower that the proportion they represent in the real population. Therefore, we do not believe the lack of this information is affecting the results. However, as with every observational study, residual confounding by other unmeasured potential PC risk factors cannot be ruled out. On the other hand, dietary patterns were obtained in a different sample of women, which can limit its application to the current sample of men. However, a previous study showed that a posteriori dietary patterns can be applied to different populations resulting in different levels of adherence but still retaining validity [21]. Also, dietary intake was estimated using dietary questionnaires which, despite being validated in Spain, might be subject to measurement errors. However, we can assume that the use of a dietary history questionnaire instead of a food frequency questionnaire minimizes the occurrence of such errors. In addition, individuals with extreme values (above and below) in energy intake were discarded, which would also contribute to eliminate part of the measurement errors in the diet data. Finally, grouping foods in the exact same way was not possible due to some differences in the nutritional information collected but arbitrary decisions were avoided using the MAPAMA data on food consumption in Spain [24] and the nutritional information collected in MCC-Spain study [7] to distribute foods with ambiguous composition.

Among some of the strengths of this work it should be noted its longitudinal design that prevents reverse causation and recall bias. This is one of the few cohort studies exploring the association between *a posterior* dietary patterns and PC incidence and the first carried out in a Mediterranean country with more potential to detect associations due to its higher dietary heterogeneity in contrast with studies carried out in countries with a more uniform westernized diet [14,17,19]. Additionally, the large sample size allowed the accumulation of a sufficient number of PC cases to detect suggestive associations for global PC risk and heterogeneous effects by tumour aggressiveness. In addition, the use of dietary patterns allows considering interactions between foods and nutrients and facilitates the translation of our results to the general population. Most of the commonly used diet-quality indices are predefined (*a priori dietary patterns*) and their score systems are largely based in the existing evidence about the association between diet and cardiovascular disease, making them not fully applicable to other settings. These patterns might not be entirely representative of the population’s diet under study, preventing finding significant associations. Also, a low score in these indices represent a low consumption of healthy foods which does not necessarily correspond to a high consumption of unhealthy foods, leaving part of the relationship between diet and disease unexplored. *A posteriori* dietary patterns (extracted by applying statistical methods over the sample under study) as the ones used here, overcome most of these issues: are independent from disease and representative of the diets coexisting within the population under study. Here we used this methodology to obtain the patterns overcoming the mentioned limitations.

In conclusion, our study suggest that a high adherence to the Mediterranean diet characterized by high intake of whole fruits (not juice), vegetables, legumes, whole grains, nuts, vegetable oils or fish, is not enough to prevent PC. Additionally, the intake of foods representative of the Western diet, such as high fat dairy products, red and processed meats, refined grains, sweets, caloric drinks, convenience food and sauces, should be reduced to prevent this disease.

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Disclosure of Interests

The authors declare that they have no competing interests.

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Tables

Table 1: Baseline characteristics of the 15,296 men from the EPIC-Spain study by level of adherence to the Western, Prudent and Mediterranean dietary patterns.

			Western					**Prudent**					**Mediterranean**			
	Total	**Q1[a]**	**Q2[a]**	**Q3[a]**	**Q4[a]**	**p[b]**	**Q1[a]**	**Q2[a]**	**Q3[a]**	**Q4[a]**	**p[b]**	**Q1[a]**	**Q2[a]**	**Q3[a]**	**Q4[a]**	**p[b]**
	n= 15296	**n= 2328**	**n= 3573**	**n= 4292**	**n= 5103**		**n= 3559**	**n= 4183**	**n= 3825**	**n= 3729**		**n= 2232**	**n= 3162**	**n= 4100**	**n= 5802**	
Alcohol (gr/day) median(IQR)[c]	33.92 (14.83; 59.82)	30.71 (12.00; 55.95)	33.85 (15.19; 60.73)	35.78 (16.08; 62.63)	33.36 (14.69; 58.96)	<0.001	38.10 (16.14; 67.89)	35.34 (15.65; 61.70)	33.31 (15.00; 57.42)	28.85 (13.38; 52.47)	<0.001	31.78 (11.81; 60.03)	32.50 (13.50; 57.29)	33.75 (14.36; 60.92)	35.16 (17.51; 60.50)	<0.001
Energy (kcal/day) median(IQR)[c]	2491 (2093; 2962)	2078 (1721; 2465)	2319 (1975; 2743)	2475 (2126; 2911)	2838 (2426; 3279)	<0.001	2276 (1916; 2740)	2523 (2128; 2977)	2547 (2136; 3026)	2601 (2213; 3055)	<0.001	2045 (1689; 2465)	2257 (1925; 2659)	2442 (2096; 2860)	2813 (2437; 3255)	<0.001
BMI (kg/m^2) median(IQR)[c]	28.16 (26.16; 30.41)	28.44 (26.35; 30.77)	28.25 (26.31; 30.54)	28.22 (26.22; 30.41)	27.94 (25.94; 30.15)	<0.001	28.34 (26.26; 30.54)	28.15 (26.17; 30.52)	28.20 (26.27; 30.47)	27.91 (26.01; 30.06)	<0.001	28.34 (26.11; 30.63)	28.22 (26.14; 30.43)	28.18 (26.18; 30.46)	28.05 (26.18; 30.30)	0.342
Height (cm) median(IQR)[c]	169.00 (164.80; 173.10)	168.10 (164.00; 172.40)	169.00 (164.80; 173.00)	168.80 (164.70; 173.20)	169.40 (165.00; 173.50)	0.000	168.50 (164.40; 172.80)	168.90 (164.50; 173.00)	169.00 (165.00; 173.40)	169.50 (165.40; 173.70)	0.000	168.40 (164.30; 172.80)	168.90 (164.50; 173.00)	168.70 (164.70; 173.00)	169.30 (165.00; 173.50)	0.000
Age at recruitment (years) median(IQR)	49.92 (44.67; 56.59)	52.87 (46.87; 59.44)	51.20 (45.47; 57.72)	50.05 (44.88; 56.56)	47.79 (43.40; 53.78)	<0.001	50.58 (45.07; 57.95)	49.84 (44.70; 56.55)	49.93 (44.66; 56.31)	49.36 (44.35; 55.51)	<0.001	50.60 (44.41; 58.26)	50.14 (44.83; 57.44)	49.93 (44.71; 56.53)	49.61 (44.72; 55.61)	<0.001
Prostate Cancer						0.246					0.565					0.847
No	14687 (96%)	2229 (96%)	3423 (96%)	4112 (96%)	4923 (96%)		3404 (96%)	4024 (96%)	3680 (96%)	3579 (96%)		2145 (96%)	3044 (96%)	3933 (96%)	5565 (96%)	
Yes	609 (4%)	99 (4%)	150 (4%)	180 (4%)	180 (4%)		155 (4%)	159 (4%)	145 (4%)	150 (4%)		87 (4%)	118 (4%)	167 (4%)	237 (4%)	
Gleason Grade among cases n(%)						0.064					0.470					0.249
6	239 (39%)	40 (40%)	53 (35%)	70 (39%)	76 (42%)		63 (41%)	62 (39%)	55 (38%)	59 (39%)		34 (39%)	49 (42%)	62 (37%)	94 (40%)	
7	138 (23%)	27 (27%)	36 (24%)	37 (21%)	38 (21%)		30 (19%)	31 (19%)	41 (28%)	36 (24%)		13 (15%)	32 (27%)	39 (23%)	54 (23%)	
8	54 (9%)	3 (3%)	16 (11%)	17 (9%)	18 (10%)		16 (10%)	19 (12%)	10 (7%)	9 (6%)		11 (13%)	7 (6%)	13 (8%)	23 (10%)	
9	20 (3%)	1 (1%)	5 (3%)	12 (7%)	2 (1%)		6 (4%)	6 (4%)	4 (3%)	4 (3%)		6 (7%)	1 (1%)	6 (4%)	7 (3%)	
10	3 (0%)	0 (0%)	0 (0%)	2 (1%)	1 (1%)		2 (1%)	1 (1%)	0 (0%)	0 (0%)		1 (1%)	0 (0%)	0 (0%)	2 (1%)	
Unknown	155 (25%)	28 (28%)	40 (27%)	42 (23%)	45 (25%)		38 (25%)	40 (25%)	35 (24%)	42 (28%)		22 (25%)	29 (25%)	47 (28%)	57 (24%)	
ISUP Grade among cases n(%)						0.052					0.426					0.166
1	235 (39%)	40 (40%)	52 (35%)	69 (38%)	74 (41%)		62 (40%)	62 (39%)	53 (37%)	58 (39%)		34 (39%)	49 (42%)	61 (37%)	91 (38%)	
2	95 (16%)	19 (19%)	25 (17%)	22 (12%)	29 (16%)		18 (12%)	22 (14%)	27 (19%)	28 (19%)		12 (14%)	21 (18%)	24 (14%)	38 (16%)	
3	41 (7%)	8 (8%)	10 (7%)	14 (8%)	9 (5%)		10 (6%)	9 (6%)	14 (10%)	8 (5%)		1 (1%)	10 (8%)	15 (9%)	15 (6%)	
4	54 (9%)	3 (3%)	16 (11%)	17 (9%)	18 (10%)		16 (10%)	19 (12%)	10 (7%)	9 (6%)		11 (13%)	7 (6%)	13 (8%)	23 (10%)	
5	23 (4%)	1 (1%)	5 (3%)	14 (8%)	3 (2%)		8 (5%)	7 (4%)	4 (3%)	4 (3%)		7 (8%)	1 (1%)	6 (4%)	9 (4%)	
Unknown	161 (26%)	28 (28%)	42 (28%)	44 (24%)	47 (26%)		41 (26%)	40 (25%)	37 (26%)	43 (29%)		22 (25%)	30 (25%)	48 (29%)	61 (26%)	
Physical Activity n(%)						0.001					<0.001					<0.001
Inactive	4109 (27%)	689 (30%)	1013 (28%)	1126 (26%)	1281 (25%)		901 (25%)	1059 (25%)	1020 (27%)	1129 (30%)		678 (30%)	890 (28%)	1077 (26%)	1464 (25%)	
Moderately inactive	5057 (33%)	769 (33%)	1161 (32%)	1388 (32%)	1739 (34%)		1174 (33%)	1405 (34%)	1256 (33%)	1222 (33%)		760 (34%)	1061 (34%)	1327 (32%)	1909 (33%)	
Moderately active	4922 (32%)	710 (30%)	1134 (32%)	1424 (33%)	1654 (32%)		1214 (34%)	1398 (33%)	1233 (32%)	1077 (29%)		656 (29%)	979 (31%)	1352 (33%)	1935 (33%)	
Active	1208 (8%)	160 (7%)	265 (7%)	354 (8%)	429 (8%)		270 (8%)	321 (8%)	316 (8%)	301 (8%)		138 (6%)	232 (7%)	344 (8%)	494 (9%)	
Smoking n(%)						<0.001					<0.001					<0.001
Never Smoker	4471 (29%)	680 (29%)	1070 (30%)	1292 (30%)	1429 (28%)		978 (27%)	1285 (31%)	1106 (29%)	1102 (30%)		579 (26%)	887 (28%)	1205 (29%)	1800 (31%)	
Former Smoker	4676 (31%)	876 (38%)	1095 (31%)	1265 (29%)	1440 (28%)		939 (26%)	1161 (28%)	1232 (32%)	1344 (36%)		628 (28%)	940 (30%)	1241 (30%)	1867 (32%)	
Current Smoker	6141 (40%)	771 (33%)	1407 (39%)	1732 (40%)	2231 (44%)		1639 (46%)	1735 (41%)	1486 (39%)	1281 (34%)		1024 (46%)	1334 (42%)	1652 (40%)	2131 (37%)	

Unknown	8 (0%)	1 (0%)	1 (0%)	3 (0%)	3 (0%)		3 (0%)	2 (0%)	1 (0%)	2 (0%)		1 (0%)	1 (0%)	2 (0%)	4 (0%)	
Education n(%)						<0.001					<0.001					0.002
No formal Education	4040 (26%)	664 (29%)	969 (27%)	1162 (27%)	1245 (24%)		1160 (33%)	1166 (28%)	952 (25%)	762 (20%)		643 (29%)	873 (28%)	1079 (26%)	1445 (25%)	
Primary School	5701 (37%)	798 (34%)	1277 (36%)	1603 (37%)	2023 (40%)		1358 (38%)	1643 (39%)	1455 (38%)	1245 (33%)		807 (36%)	1105 (35%)	1576 (38%)	2213 (38%)	
Secondary/Technical School	3192 (21%)	457 (20%)	791 (22%)	868 (20%)	1076 (21%)		639 (18%)	811 (19%)	834 (22%)	908 (24%)		435 (19%)	701 (22%)	822 (20%)	1234 (21%)	
University or more	2283 (15%)	401 (17%)	513 (14%)	641 (15%)	728 (14%)		375 (11%)	539 (13%)	569 (15%)	800 (21%)		339 (15%)	466 (15%)	598 (15%)	880 (15%)	
Unknown	80 (1%)	8 (0%)	23 (1%)	18 (0%)	31 (1%)		27 (1%)	24 (1%)	15 (0%)	14 (0%)		8 (0%)	17 (1%)	25 (1%)	30 (1%)	

[a] Q1: First quartile of adherence (least adherent); Q2: Second quartile of adherence; Q3: Third quartile of adherence; Q4: Fourth quartile of adherence (most adherent).

[b] Chi-squared tests for qualitative variables (excluding missing values) and Kruskal-Wallis tests for quantitative variables

[c] Alcohol was missing for 117 (0.8%) healthy individuals and for 6(1.18%) prostate cancer cases.

Table 2: Crude and adjusted hazard ratio for the association between prostate cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns.

	Full Sample (Crude) n=15296					Full Sample (Adjusted) n=15131				
				(95%CI)					(95%CI)	
	Person/time	Number of events	HR[a,b]	LL	UL	Person/time	Number of events	HR[a,c]	LL	UL
	242416	**609**				**239797**	**604**			
WESTERN										
Quartiles										
Q1[d]	36363	99	1			35999	99	1		
Q2[d]	56562	150	1.07	0.83	1.38	55964	150	1.11	0.85	1.44
Q3[d]	68045	180	1.17	0.92	1.50	67496	178	1.21	0.92	1.60
Q4[d]	81447	180	1.21	0.94	1.56	80338	177	1.29	0.96	1.72
p-trend			0.090					0.074		
1SD-increase			1.07	0.97	1.17			1.09	0.97	1.21
PRUDENT										
Quartiles										
Q1[d]	36363	155	1.00			53705	155	1.00		
Q2[d]	56562	159	0.87	0.70	1.09	65592	159	0.89	0.71	1.11
Q3[d]	68045	145	0.88	0.70	1.11	60838	141	0.90	0.71	1.14
Q4[d]	81447	150	1.00	0.79	1.25	59662	149	1.08	0.84	1.38
p-trend			0.990					0.601		
1SD-increase			1.00	0.92	1.09			1.03	0.94	1.13
MEDITERRANEAN										
Quartiles										
Q1[d]	36363	87	1.00			33588	87	1.00		
Q2[d]	56562	118	0.90	0.68	1.19	49301	116	0.89	0.67	1.19
Q3[d]	68045	167	1.00	0.77	1.30	64653	167	1.02	0.78	1.33
Q4[d]	81447	237	1.02	0.79	1.31	92256	234	1.05	0.79	1.38
p-trend			0.517					0.420		
1SD-increase			1.03	0.94	1.12			1.03	0.93	1.15

[a] Proportional hazards assumption was fulfilled in all cases.
[b] HR of prostate cancer stratified by centre and age in 5-year periods.
[c] HR of prostate cancer stratified by centre and age in 5-year periods and adjusted by energy intake, BMI, height and education at recruitment.
[d] Q1: First quartile of adherence (least adherent); Q2: Second quartile of adherence; Q3: Third quartile of adherence; Q4: Fourth quartile of adherence (most adherent).

Table 3: Hazard ratio for the association between prostate cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns by tumour aggressiveness according to Gleason grade grouped as =6 vs >6 and ISUP 1+2 vs ISUP 3+4+5 categories.

	Gleason =6					Gleason >6					ISUP=1+2[a]					ISUP=3+4+5[a]				
		n=14763							n=14741			n=14854					n=14644			
	Person/ time	Number of events	HR[b,c]	(95%CI) LL	UL	Person/ time	Number of events	HR[b,c]	(95%CI) LL	UL	Person/ time	Number of events	HR[b,c]	(95%CI) LL	UL	Person/ time	Number of events	HR[b,c]	(95%CI) LL	UL
	236006	**236**				**235842**	**214**				**237156**	**327**				**234649**	**117**			
WESTERN																				
Quartiles																				
Q1[d]	35393	40	1			35328	31	1			35640	59	1			35081	12	1		
Q2[d]	54946	53	0.91	0.59	1.39	55025	57	1.38	0.87	2.19	55234	77	0.92	0.64	1.31	54718	31	1.97	0.98	3.93
Q3[d]	66401	69	1.03	0.66	1.59	66411	68	1.61	1.00	2.59	66676	90	0.99	0.68	1.43	66128	45	2.72	1.35	5.51
Q4[d]	79266	74	1.08	0.68	1.71	79079	58	1.60	0.96	2.67	79607	101	1.11	0.75	1.62	78722	29	2.29	1.07	4.92
p-trend			0.533					0.080					0.445					0.040		
1SD-increase			1.06	0.89	1.26			1.11	0.92	1.34			1.06	0.91	1.22			1.16	0.89	1.51
PRUDENT																				
Quartiles																				
Q1[d]	52796	63	1.00			52709	54	1.00			53000	80	1.00			52489	34	1.00		
Q2[d]	64595	62	0.81	0.57	1.16	64545	57	0.93	0.63	1.35	64889	84	0.87	0.64	1.19	64250	35	0.95	0.59	1.53
Q3[d]	59893	53	0.77	0.53	1.13	59927	54	1.01	0.68	1.50	60212	78	0.90	0.65	1.25	59592	27	0.86	0.51	1.46
Q4[d]	58722	58	0.94	0.63	1.39	58661	49	1.05	0.68	1.61	59054	85	1.09	0.77	1.52	58319	21	0.80	0.44	1.46
p-trend			0.681					0.737					0.606					0.433		
1SD-increase			0.94	0.80	1.09			1.06	0.90	1.24			1.01	0.89	1.15			0.95	0.76	1.19
MEDITERRANEAN																				
Quartiles																				
Q1[d]	33057	34	1.00			33047	31	1.00			33195	46	1.00			32910	19	1.00		
Q2[d]	48637	48	0.92	0.59	1.43	48527	40	0.88	0.55	1.43	48876	69	0.99	0.67	1.44	48280	18	0.66	0.34	1.26
Q3[d]	63558	62	0.90	0.59	1.39	63536	58	1.02	0.65	1.61	63869	85	0.93	0.64	1.35	63215	34	1.02	0.57	1.82
Q4[d]	90754	92	0.93	0.60	1.45	90731	85	1.17	0.74	1.87	91216	127	1.00	0.68	1.45	90245	46	1.13	0.62	2.06
p-trend			0.834					0.284					0.975					0.295		
1SD-increase			0.93	0.79	1.09			1.15	0.96	1.37			0.95	0.83	1.09			1.23	0.96	1.58

[a] ISUP 1= Gleason 3+3; ISUP 2= Gleason 3+4; ISUP 3= Gleason 4+3; ISUP 4= Gleason 4+4, 3+5, 5+3; ISUP 5= Gleason 4+5, 5+4, 5+5.

[b] Proportional hazards assumption was fulfilled in all cases.

[c] HR of prostate cancer by tumour aggressiveness stratified by centre and age in 5-year periods, adjusted by energy intake, BMI, height and education at recruitment.

[d] Q1: First quartile of adherence (least adherent); Q2: Second quartile of adherence; Q3: Third quartile of adherence; Q4: Fourth quartile of adherence (most adherent).

Figures

Figure 1. Selection process of PC cancer cases and non-cases in the Epic-Spain cohort.

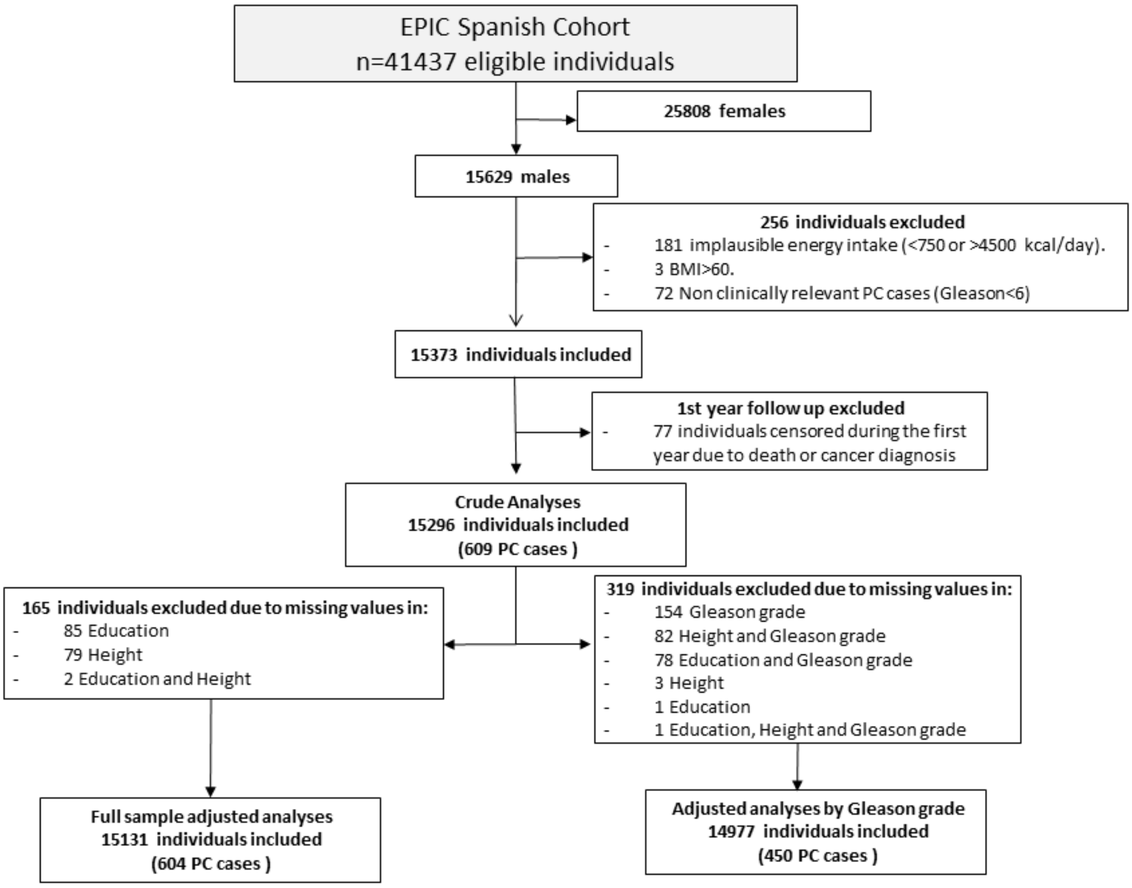
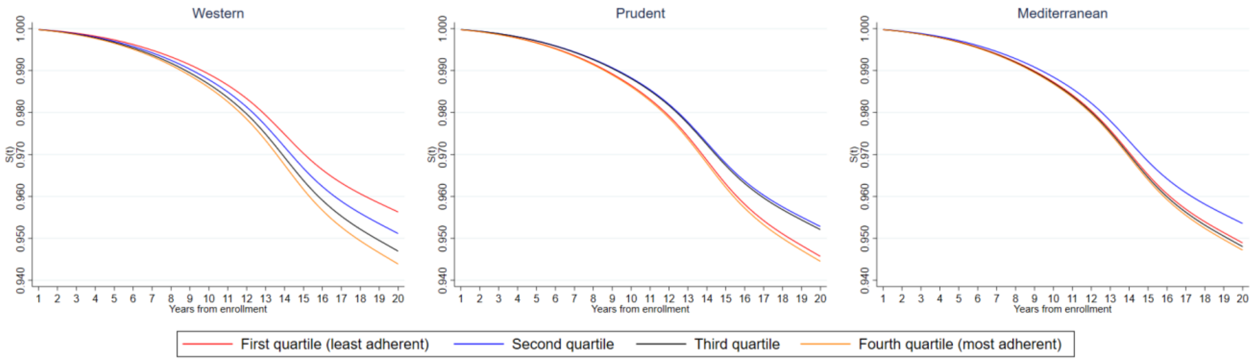


Figure 2: Standardized[a] survival curves for prostate cancer by quartiles of adherence to the Western, Prudent and Mediterranean dietary patterns.



Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
At risk	15115	15012	14902	14775	14638	14493	14316	14113	13942	13738	13506	13259	12965	12720	11742	9899	7606	4530	1860	1860

[a] By energy intake, BMI, height, education and age at recruitment and centre.

Supplementary material

Table S1: Composition of food groups based on the dietary history questionnaire of the EPIC-Spain study and component loadings obtained with the data of EPIGEICAM study [21].

FOOD GROUP	FOOD[a]	West[b]	Prud[b]	Med[b]
HIGH-FAT DAIRY	Whole-fat milk, milk, milk beverages, curd and yogurt; cream desserts; dairy creams; portion of unknown fat content diary[c].	0.60	-0.11	0.20
LOW FAT DAIRY	Semi-skimmed and skimmed milk, milk beverages, curd and yogurt; Cottage or fresh white cheese. portion of unknown fat content diary[c].	-0.49	0.60	-0.01
EGGS	Eggs.	0.19	0.08	0.16
WHITE MEAT	Poultry and game.	0.08	0.17	0.18
RED MEAT	Red meat (Pork, beef, veal, lamb, etc.); liver; entrails; hamburgers: meatballs; grounded meat; non-specified or mixed meat and derivates.	0.27	0.09	0.22
PROCESSED MEAT	Serrano ham and other cold meat; bacon; other processed meats; non-specified or mixed processed meat.	0.36	0.10	0.26
WHITE FISH	Fresh or frozen white fish (hake, sea bass, sea bream); 2/3·processed white fish; ½·fish eggs; ½·fish liver; 1/3·non classified fish and seafood.	0.01	0.22	0.34
OILY FISH	Fresh frozen or processed blue fish (tuna, swordfish, sardines, anchovies, salmon); 2/3·processed blue fish; ½·fish eggs; ½·fish liver; 1/3·non classified fish and seafood.	0.05	0.24	0.44
SEAFOOD/SHELLFISH	Crustaceans and molluscs; 1/3·non classified fish and seafood.	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. Cabbage; mushrooms; grain or pod vegetables; onion and garlic; tail or sprout vegetables; mixed salads or vegetables; non-classified vegetables.	-0.04	0.40	0.42
LEGUMES	Peas, lentils, chickpeas, beans, and broad beans	0.21	0.15	0.34
POTATOES	Potatoes and other tubers.	0.17	0.25	0.40
FRUITS	All kind of fruits.	-0.07	0.31	0.31
NUTS	Nuts and seeds.	0.18	0.22	0.29
REFINED GRAINS	Flour, flakes, starch, semolina flour; pasta, rice, other unspecified or combined grains; pasta; other grains; cereal-based products such as pasta; 1/3·unspecified or mixed bread, biscuits, cookies; ½·unspecified bread; White bread; 1/3·rusks, unspecified cookies; ½·biscuits, white cookies; ½·unspecified or combined dough or pastry; bread and pizza dough; 2/3·unspecified white bread, biscuits, or mixes.	0.37	0.15	0.23
WHOLE GRAINS	Unspecified or combined cereal products: ½ · unspecified bread; non-white bread; breakfast cereals; 1/3 · unspecified or mixed bread, biscuits, biscuits; 2/3 · non-white bread, biscuit, unspecified or mixed biscuits; 1/3 · rusks, unspecified biscuits; ½ · biscuits, not white cookies.	-0.43	0.47	0.06
OLIVES AND VEGETABLE OIL	Olives; vegetable oils.	0.12	0.19	0.34
OTHER EDIBLE FATS	Margarine; butter; oil of marine origin; other animal edible fats.	0.22	0.02	0.11
SWEETS	1/3 * biscuits, unspecified cookies; ½ * biscuits, white cookies; 1/2 · biscuits, non-white biscuits; ½ · unspecified or combined dough or pastry; cupcakes; 1/3 · unspecified or mixed bread, biscuits, biscuits; 1/3 · white bread, biscotti, cookies not specified or mixed; 1/3 · non-white bread, biscuit, cookies not specified or	0.35	0.18	0.05

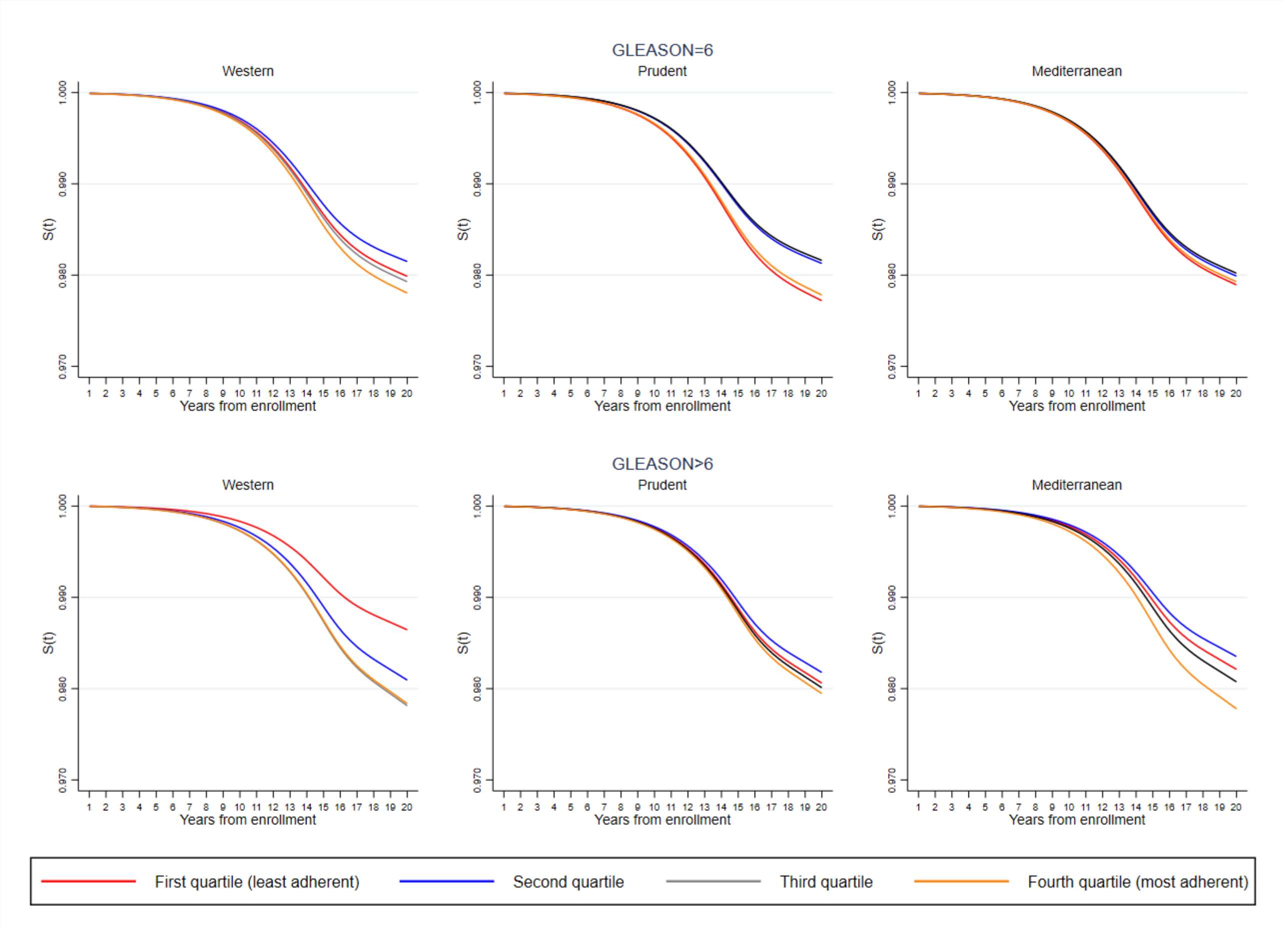
	mixed; chocolate, candy, bar, pasta, confectionery; non-chocolate confectionery, candied fruit; sorbet, water ice; cakes and cookies			
SUGARY	Jam, Honey, Sugar and fruit in sugar syrup.	0.24	0.05	0.00
JUICES	Vegetable and fruit juices.	0.25	0.67	-0.39
CALORIC DRINKS	Sugar-sweetened soft drinks; unclassified non-alcoholic drinks.	0.74	0.21	-0.25
CONVENIENCE FOOD AND SAUCES	Crackers and snack cookies; Egg derivates; 1/3·processed white fish; 1/3·processed blue fish; tomato sauces; other/unsorted or mixed sauces; aioli sauces; mayonnaise and other creamy sauces; snacks; non-dairy creams; fried products; ½·condiments and sauces not classified; vegetarian products and dishes; other dietary products.	0.47	0.12	0.24

[a] Log-transformed centred intake in grams.

[b] West=Western; Prud=Prudent; Med=Mediterranean.

[c] For non-cancer cases: Portion in high-fat dairy=0.65·Unknown and Portion in low-fat dairy=0.35·Unknown
For PC cancer cases: Portion in high-fat dairy=0.62·Unknown and Portion in low-fat dairy=0.38·Unknown
For cases of other tumours (Including PC): Portion in high-fat dairy=0.68·Unknown and Portion in low-fat dairy=0.32·Unknown

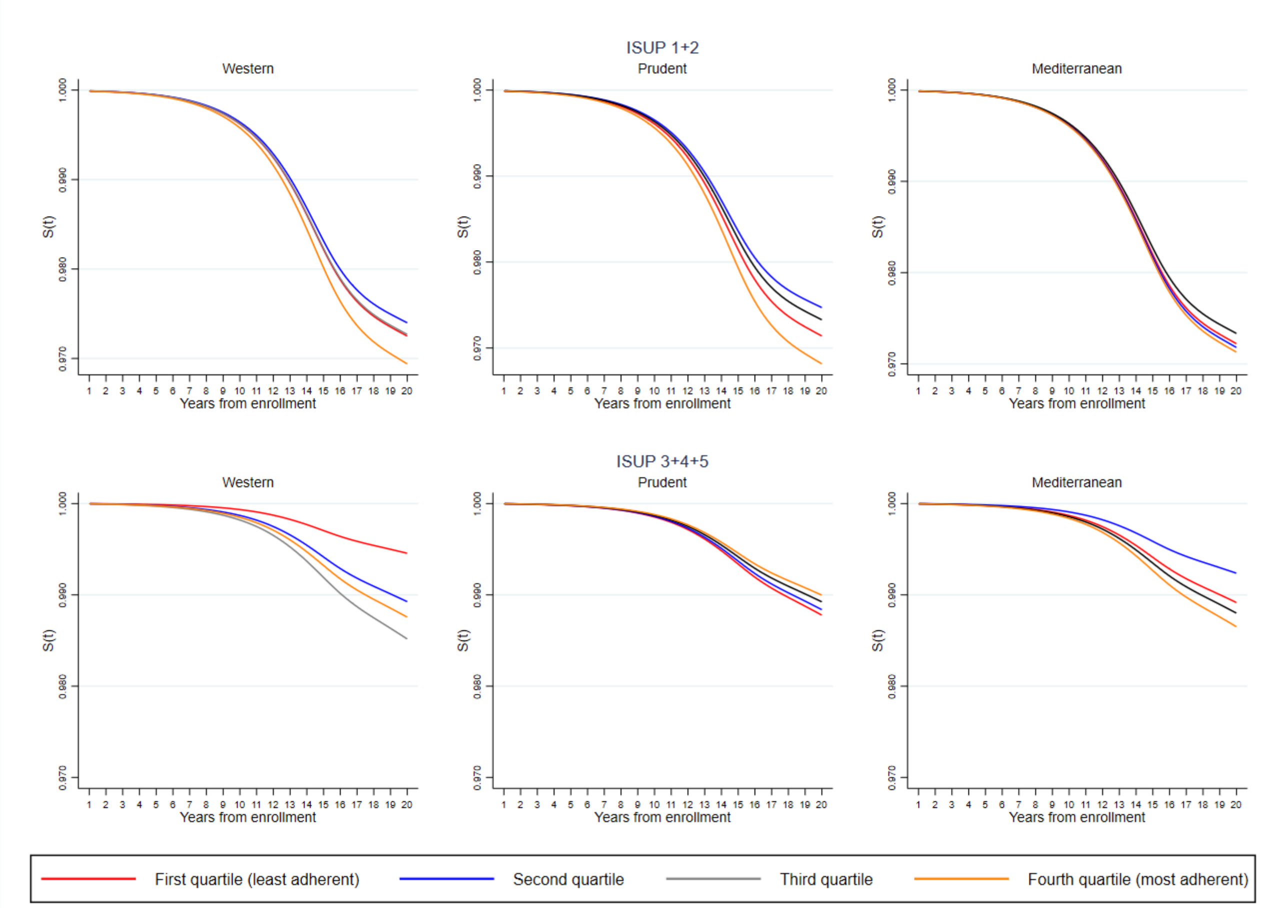
Figure S1: Standardized[a] survival curves for prostate cancer by quartiles of adherence to the Western, Prudent and Mediterranean dietary patterns by tumour aggressiveness according to Gleason grade grouped as =6 vs >6.



Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
GLEASON==6 At risk	14753	14656	14555	14440	14322	14202	14045	13861	13703	13532	13327	13106	12843	12631	11687	9870	7599	4530	1860	1860
GLEASON>6 At risk	14730	14632	14529	14416	14297	14175	14022	13844	13694	13520	13323	13108	12853	12634	11690	9874	7603	4528	1860	1860

[a] By energy intake, BMI, height, education and age at recruitment and centre.

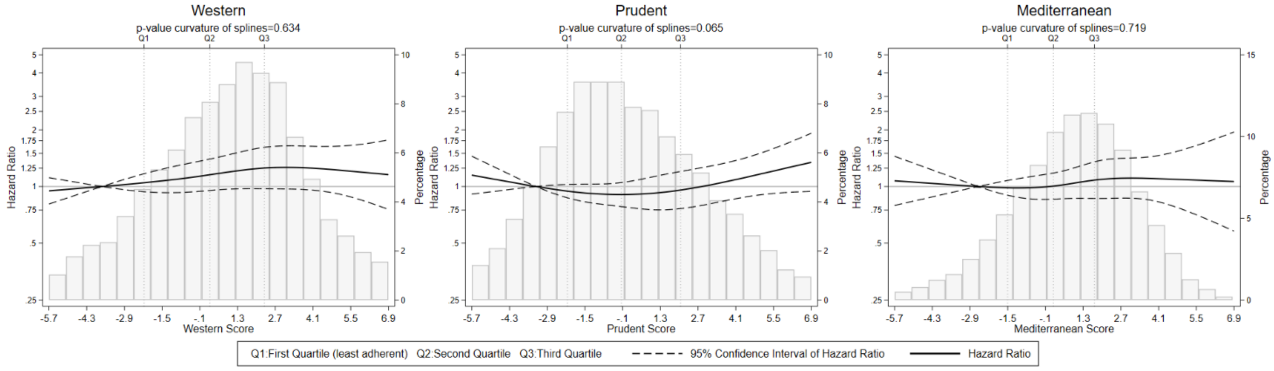
Figure S2: Standardized[a] survival curves for prostate cancer by quartiles of adherence to the Western, Prudent and Mediterranean dietary patterns by tumour aggressiveness according to Gleason grade grouped according to the ISUP[b] classification 1+2 vs ISUP 3+4+5.



Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
ISUP 1+2 **At risk**	14844	14747	14645	14530	14411	14288	14131	13946	13786	13608	13397	13163	12890	12663	11705	9879	7602	4530	1860	1860
ISUP 3+4+5 **At risk**	14633	14535	14434	14321	14203	14085	13933	13756	13608	13444	13253	13051	12806	12602	11672	9865	7600	4528	1860	1860

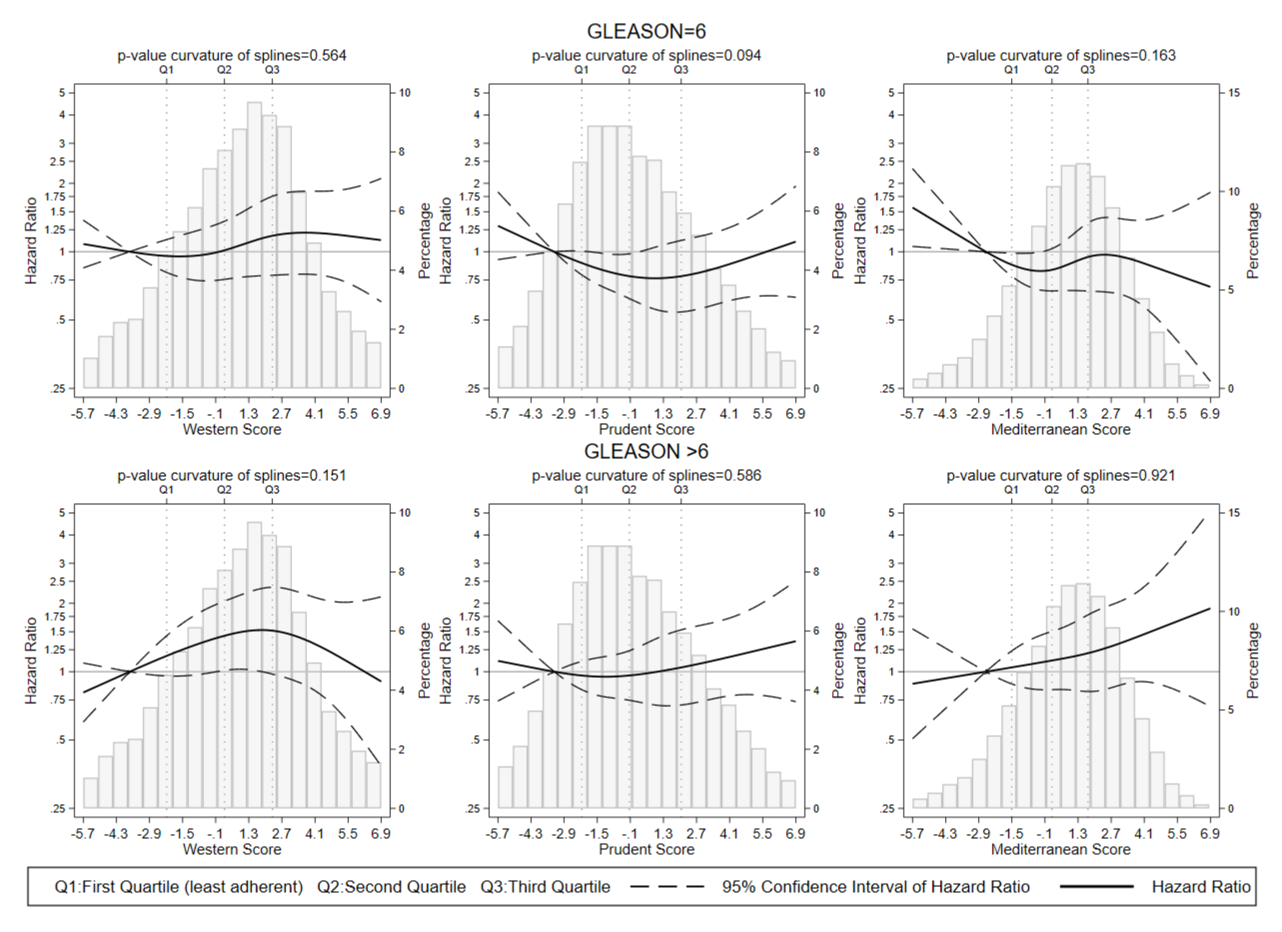
[a] By energy intake, BMI, height, education and age at recruitment and centre.
[b] ISUP 1= Gleason 3+3; ISUP 2= Gleason 3+4; ISUP 3= Gleason 4+3; ISUP 4= Gleason 4+4, 3+5, 5+3; ISUP 5= Gleason 4+5, 5+4, 5+5.

Figure S3: Non-linear association[a] between prostate cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns.



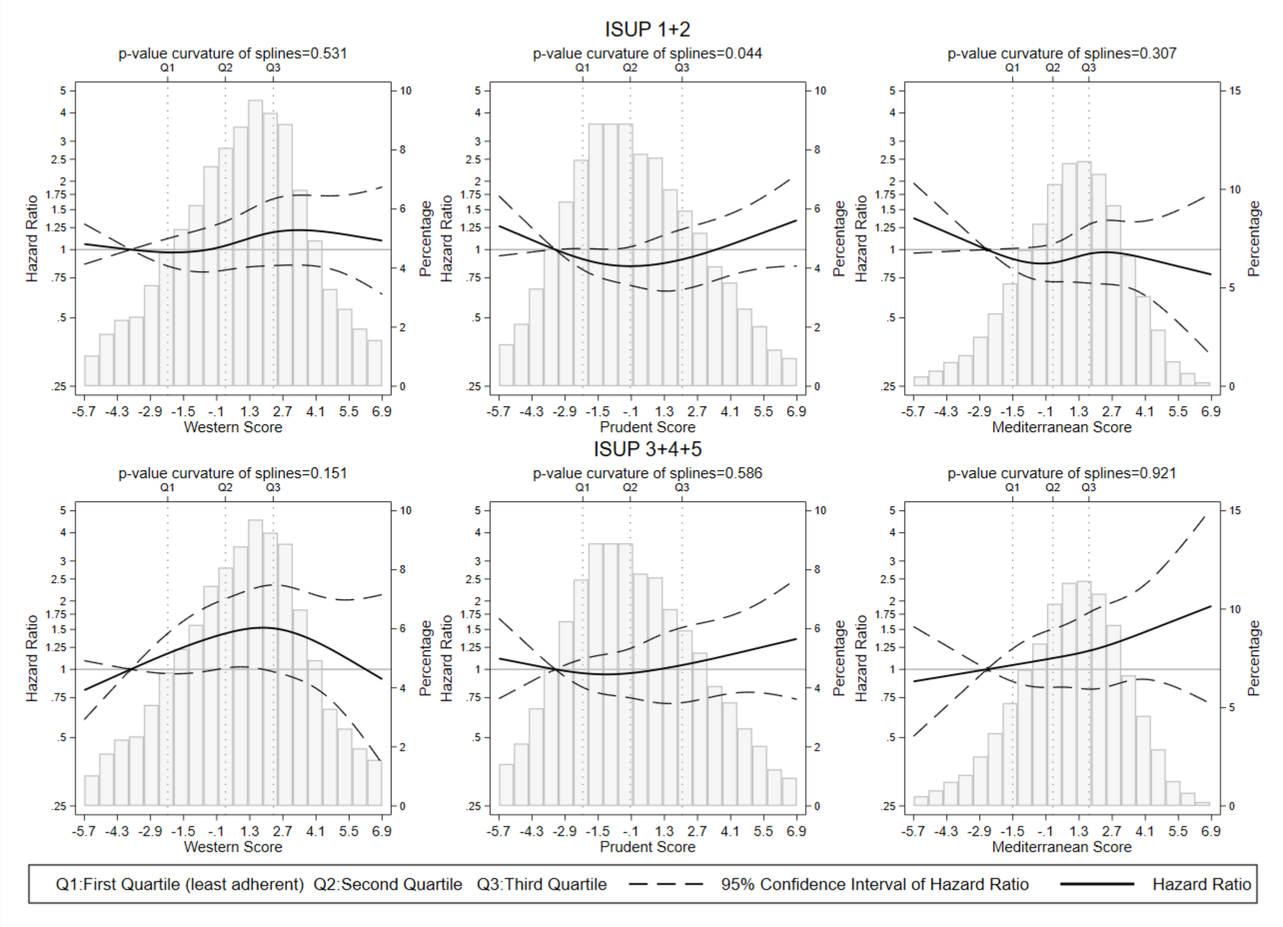
[a] Adjusted by energy intake, BMI, height, education and age at recruitment and centre. Reference set at the median of the first quartile interval (-3.73 for the Western pattern, -3.31 for the Prudent pattern and -2.60 for the Mediterranean pattern).

Figure S4: Non-linear association between prostate cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns by tumour aggressiveness according to Gleason grade grouped as =6 vs >6.



[a] Adjusted by energy intake, BMI, height, education and age at recruitment and centre. Reference set at the median of the first quartile interval (Gleason=6: -3.74 for the Western pattern, -3.31 for the Prudent pattern and -2.60 for the Mediterranean pattern; Gleason >6: -3.74 for the Western pattern, -3.31 for the Prudent pattern and -2.60 for the Mediterranean pattern).

Figure S5: Non-linear association[a] between prostate cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns by tumour aggressiveness according to Gleason grade grouped according to the ISUP[b] classification 1+2 vs ISUP 3+4+5.



[a] Adjusted by energy intake, BMI, height, education and age at recruitment and centre. Reference set at the median of the first quartile interval (ISUP 1+2: -3.74 for the Western pattern, -3.32 for the Prudent pattern and -2.60 for the Mediterranean pattern; Gleason >6: -3.74 for the Western pattern, -3.31 for the Prudent pattern and -2.60 for the Mediterranean pattern).
[b] ISUP 1= Gleason 3+3; ISUP 2= Gleason 3+4; ISUP 3= Gleason 4+3; ISUP 4= Gleason 4+4, 3+5, 5+3; ISUP 5= Gleason 4+5, 5+4, 5+5.