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Dietary inflammatory index (DII) and risk of prostate cancer in a case-control study among Black and White US Veteran men

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Abstract

BACKGROUND: We hypothesized a pro-inflammatory diet would be associated with higher prostate cancer (PC) risk.

METHODS: We prospectively recruited incident PC cases (n=254) and controls (n=328) at the Durham Veteran Affairs, from 2007–2018. From a self-completed 61-item Food Frequency Questionnaire, we calculated dietary inflammatory index (DII®) scores with and without supplements. We examined the association between DII scores with and without supplements and

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Disclosure of Potential Conflict of Interest:

Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on activities of CHI, nor has CHI exerted any influence on this project.

No other author has a potential conflict to disclose.

overall PC risk using logistic regression and risk of low-grade PC (grade group 1) and high-grade PC (grade group 2–5) with multinomial logistic regression.

RESULTS: Cases were more likely to be Black (58% vs. 42%), had higher PSA (6.4 vs. 0.8 ng/ml), lower BMI (29.1 vs. 30.6 kg/m^2) and were older (64 vs. 62 years) versus controls (all p<0.01). Both black controls and cases had higher DII scores with and without supplements, though the DII scores with supplements in controls was not significant. On multivariable analysis, there were no associations between DII with or without supplements and overall PC risk (p-trend=0.14, p-trend=0.09, respectively) or low-grade PC (p-trend=0.72, p-trend=0.47, respectively). Higher DII scores with (p-trend=0.04) and without supplements (p =0.08) were associated with high-grade PC, though the association for DII without supplements was not significant.

CONCLUSIONS: A pro-inflammatory diet was more common among Black men and associated with high-grade PC in our case-control study. The degree to which a pro-inflammatory diet contributes to PC race disparities warrants further study. If confirmed, studies should test whether a low inflammatory diet can prevent high-grade PC, particularly among Black men.

Keywords

prostate cancer; diet; dietary inflammatory index

INTRODUCTION

Prostate cancer (PC) is one of the most common cancers among men worldwide,[1] including in the USA.[2] Besides age, race and family history of PC, modifiable etiologic factors associated with PC risk are not well known. Diet encompasses a number of environmental factors that could influence the development of PC.[3] However, the exact food constituents that increase or decrease risk remain unclear given often conflicting results in the literature (reviewed in[4]). An alternative to examining specific food constituents is to examine dietary patterns,[5, 6] including ones that may play a role in modulating inflammation,[7, 8] a potential mechanism associated with PC development.

Evidence suggests both systemic[9] and prostatic inflammation[10] may play a role in prostate carcinogenesis,[11] and that diet plays a central part in the regulation of chronic inflammation. A Western-type diet high in red meat, high-fat dairy products, refined grains and simple carbohydrates has been associated with higher levels of inflammatory markers,[12] whereas the Mediterranean diet, high in fruits and vegetables, omega-3 polyunsaturated fatty acids, fish and fiber has been linked to lower levels of inflammation.[13] Given the potential role of inflammation in PC, this gives rise to the hypothesis that a pro-inflammatory diet may promote PC risk.

The dietary inflammatory index (DII®) was developed[14] and validated[15] to assess the overall quality of the diet with respect to its inflammatory potential. The DII was developed from a careful review and scoring of the scientific literature on diet and inflammation, and subsequently validated on a prospective observational study of healthy participants followed for 1 year.[15, 16] Briefly, the DII represents a refined scoring algorithm based on extensive

review of the literature from 1950 to 2010 (10). Qualifying articles were scored according to whether each dietary parameter increased (+1), decreased (−1) or had no (0) effect on six inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein. Based on this search, the authors created a tool for assessing the inflammatory potential of the diet based on forty-five food parameters, that can be applied to any population in which dietary data have been collected.[14]

To date, several case-control studies[17–21] and two prospective studies[22, 23] examined the relationship between DII and PC risk. Among Italian,[17], Iranian,[18] Jamaican,[19] Canadian,[20] Argentinian,[21] and French men,[22] a higher DII score was associated with a higher risk of PC, though the associations did not reach statistical significance in some studies and the number of men included was often quite small. However, none of the studies examined DII and PC aggressiveness with two exceptions, one was a case-control study among Mexican men, which found no associations between DII score and PC risk and aggressiveness.[24] The second study among a prospective cohort of Californian men found a higher DII was associated with higher risk of high-grade PC, however they found a non-linear relationship, i.e. associations became null in the fourth quartile.[23] Therefore, it is not clear whether the DII is associated with PC aggressiveness.

We examined the association between DII and PC risk in a case-control study of Black and White men at the Durham Veteran Affairs Medical Center. Furthermore, we assessed whether the intake of supplements modified this association. Given that inflammation is known to be more prevalent in Black men,[10] we hypothesized that DII scores are higher in Black men and that the association between PC risk and DII is stronger in Black men compared to White men, but that higher DII would be associated with increased PC risk and aggressiveness in both races.

MATERIAL AND METHODS

Data Collection and Study Population

After receiving approval from the institutional review board and written informed consent from all men, we obtained data from an ongoing case-control study of men at the Durham Veterans Affair Medical Center (DVAMC). Methods for identification and accrual of participants have been described elsewhere.[25, 26] Men were recruited between January 2007 and January 2018 from the urology, internal medicine, and dermatology clinics at the DVAMC. Eligible men had no prior history of PC and had a prostate specific antigen (PSA) test in the year prior to enrollment.

Cases were selected from men who underwent biopsy and were found to have cancer. Cases were ascertained at the time of biopsy and thus not susceptible to post-diagnosis dietary changes often undertaken by people newly diagnosed with cancer.[27, 28] Men were approached for enrollment prior to biopsy and most often completed questionnaires after the biopsy but prior to knowledge of the biopsy results. Of note, all questionnaires were self-administered and median (IQR) time between biopsy and questionnaire completion was 3 days (0,15). Given this timeframe, although the date on which men were informed of their biopsy results was not recorded, it is likely that only a subset of men knew their cancer

status before completing the questionnaire. Of the 1,617 men undergoing biopsy, 1,250 (77% response rate) consented to participate in the study. Of the men undergoing biopsy, we only evaluated those with a positive biopsy for PC (n=656; 52% of biopsies).

Controls were similar to the cases, in that they had a PSA within a year and no history of PC. However, they were not recommended to undergo a biopsy. Of 1,149 controls screened, 589 controls (51% response rate) consented.

A total of 652 cases and controls completed the food frequency questionnaire. Men with missing data on self-reported smoking history (n=45), caloric intake from the FFQ (n=3) or PSA (n=2) were excluded. Finally, we dropped men with extreme values of caloric intake (n=20) using Tukey fence's approach (less than the 25th percentile – 1.5*interquartile range or greater than the 75th percentile + 1.5*interquartile range), resulting in a final study population of 582 men (Figure 1).

Height and weight were measured by trained personnel. Participants were asked to fill out the 61-item Harvard Food Frequency Questionnaire (FFQ),[29] as well as a questionnaire detailing family, medical, and social history. All questionnaires were self-administered and either filled out the day of the biopsy or returned by mail usually prior to the patient knowing the biopsy outcome. From the FFQ, we calculated the dietary inflammatory index (DII) as described previously.[14, 15] In brief, the DII is a weighted index of the degree to which the diet influences known serum inflammatory markers. Each food item is given a corresponding inflammatory score with the total DII representing the summed scores across all food parameters. It is modeled to create a symmetric distribution with values centered on 0 with higher scores representing more inflammation. It has been subsequently validated in four studies among different populations showing strong correlations with a variety of serum inflammatory biomarkers.[15, 30–34] The exactly methodology of how the DII was derived is explained in more detail in the DII Methods paper.[14]

Using the FFQ, we calculated the DII based on energy-adjusted intake of the 33 single food parameters of the 45 possible food parameters that were available from the FFQ using the energy density approach, which calculated the DII per 1000 kcal of energy.[35] The 33 food parameters available for DII calculation in this study were vitamin B_{12}, vitamin B_6, β-carotene, carbohydrate, cholesterol, fat, fibre, folic acid, iron, magnesium, monounsaturated fat acids (MUFA), niacin, protein, polyunsaturated fatty acids (PUFA), omega 3 and 6, riboflavin, saturated fat acids (SFA), selenium, thiamin, vitamin A, vitamin C, vitamin E, vitamin D, zinc, niacin, anthocyanidins, flavan3ol, flavones, flavonols, flavonones and caffeine. For the following parameters, supplement data were available in addition to the data from the normal diet: iron, zinc, vitamin C, B1, B2, B6, folate, Vitamin A, vitamin D, B12, Vitamin E, beta carotene, niacin, magnesium. On secondary analysis, we added supplement use to the DII calculation.

Statistical Analysis

Characteristics between cases and controls were compared using the Wilcoxon rank sum test for continuous variables and chi-squared test for categorical variables. Logistic regression was used to examine the association between DII scores with or without supplements and

PC diagnosis. Multinomial logistic regression was used to test the association between DII with or without supplements and low-grade PC (biopsy grade group 1) vs. no cancer and high-grade PC (biopsy grade group 2–5) vs. no cancer. DII was treated as a categorical variable divided into quartiles with cut-offs based on the controls. Models were fit unadjusted and adjusted for age (continuous), race (Black vs. Non-Black), BMI (continuous), smoking history (current/former smoker vs. never-smoker), and daily caloric intake (continuous).

The interaction between DII with or without supplements, BMI, and race to assess the association with PC diagnosis was tested by including the main effects and cross product term in the multivariable logistic regression. Analyses were performed using SAS® 9.4 (SAS Institute, Inc. Cary, NC). Statistical significance was two-sided with a threshold of $p<0.05$. Code availability: TO, LEH.

RESULTS

Patient Characteristics

The study cohort consisted of 328 (56%) controls and 254 (44%) cases (Table 1). Of the cases, 53% were high-grade (biopsy grade groups 2–5). Cases were more likely to be Black (58% vs. 42%, $p<0.001$), had higher PSA (6.4 vs. 0.8 ng/ml, $p<0.001$), had lower BMI (29.1 vs. 30.6 kg/m^2, $p<0.01$), and were older (64 vs. 62 years, $p<0.001$) compared to controls. There was no difference in smoking history, daily caloric intake, or DII with or without supplements (all $p>0.15$). DII scores, with and without supplements, were higher in Black men compared to White men, both in controls and PC cases (Table 2). In a sub-analysis among controls, we found DII was not correlated with PSA (data not shown). There was no collinearity between race and DII ($\rho = -0.16$, for race and DII with supplements; $\rho = -0.12$, for race and DII without supplements).

Primary Analysis: DII and overall PC Risk

On univariable analysis, there was no association between DII with or without supplements and overall PC diagnosis [both p-trend ≥0.18] (Table 3). There remained no association between DII with or without supplements and overall PC risk (both p-trend ≥ 0.09), after multivariable adjustment. No interaction was found between DII score with supplements and BMI (p-interaction=0.87) and race (p-interaction=0.79) in assessing the association with overall PC diagnosis. Similar results were obtained when the interactions between DII without supplements and BMI (p-interaction=0.61) and between DII without supplement and race (p-interaction=0.36) were tested.

Secondary Analysis: DII and low- and high-grade PC Risk

DII scores with supplements was not associated with risk of low-grade PC (p-trend=0.83), on unadjusted analysis (Table 3). Likewise, DII without supplements was not associated with risk of low-grade PC (p-trend=0.86). After adjustment for known potential confounders, there remained no association between DII with (p-trend=0.72) or without (p-trend=0.47) supplements and risk of low-grade PC. Regarding high-grade disease, on unadjusted analysis, each quartile of higher DII with supplements was associated with

increasing risk of high-grade disease, though the overall association approached, but did not reach, statistical significance (p-trend=0.06). After adjustment for confounders, higher DII scores with supplements were associated with statistically significantly increased risk of high-grade PC (p-trend=0.04). While overall similar patterns were seen for DII without supplements and high-grade PC, all associations were not statistically significant (p-trend=0.21 for unadjusted and p-trend=0.08 for adjusted analyses). Similar to the primary analysis, there was no interaction between race and DII (with or without supplements) when assessing the risk of low- or high-grade PC (all p-interactions >0.24).

DISCUSSION

Evidence suggests that both systemic[9] and prostatic inflammation[36] are linked to prostate carcinogenesis, and diet may have an influence on this association.[36, 37] Indeed, some nutrients have been shown to have a pro-inflammatory (e.g. carbohydrates, cholesterol, etc.[38]) while others (e.g. isoflavone, caffeine, garlic, omega-3 fats, soya, etc.[39, 40] have an anti-inflammatory effect. Hence, we used a DII exclusively developed to assess the inflammatory index of dietary intakes among men at the Durham VA Medical Center in the USA, where 58% of PC cases were Black men. As we hypothesized, Black men had higher DII scores than White men. Among all men, higher DII was associated with a higher risk of high-grade PC compared to controls (results only reached significance for DII with supplements). However, we found no associations between DII with or without supplements and overall or low-grade PC risk. Contrary to our hypothesis, we found no interaction between race and DII with or without supplements in predicting overall PC diagnosis. If confirmed in larger cohorts, future studies should test the anti-PC activity of an anti-inflammatory diet, especially in Black men.

Several studies reported on the associations between specific diets and PC,[3] and although seven studies analyzed the link between DII and PC risk in different cohorts of men around the globe[17–24] including U.S. men. For the present study, we used the same DII score as used in those seven studies.[14]

Among the studies that previously assessed the association between DII and PC risk, six were case-control studies[17–21, 24] and two were prospective studies.[22, 23] In 2,745 Italian men (PC cases=1,294), a higher DII, either used as a continuous or categorical variable was associated with an increased risk of PC.[17] Similarly, Canadian men (72 PC cases/302 controls) with higher DII scores were at increased risk of PC using DII score both as a continuous and categorical variable.[20] In a case–control study of 462 Argentinian males (PC cases=153), a higher DII score was associated with increased odds of PC, this effect was more pronounced among obese.[21] In other studies, among Iranian (60 PC cases/60 controls; p-trend=0.15),[18] Jamaican (229 PC cases/250 controls; p-trend=0.08),[19] and French men (PC cases=123, prospective study; p-trend=0.20),[22] though a higher DII score showed a trend for an association with higher PC risk, results were not significant, as also shown in a recent pooled analysis.[41] Whether this lack of significance reflects a true lack of association or small sample sizes is unclear. We found similar results to these latter studies among U.S. veterans: non-significant associations, though the direction of the associations favored higher DII and higher PC risk. Of note, the ORs in our study were modest but potentially

clinically important, if validated, for the highest vs. lowest quartile (OR 1.53–1.57). The largest study to date, though, found no associations between higher DII and overall PC risk, even when analyses were stratified by race.[23] As such, future larger studies or a meta-analysis of the published studies is needed to better examine the potential modest, but clinically relevant possibility that a high inflammatory diet is associated with increased PC risk.

While we found overall null associations for low-grade disease, the association between DII and risk of high-grade PC was evident. However, only the association between DII with supplements and high-grade PC was statistically significant (p-trend=0.04), after adjusting for confounders. There are only two other studies that tested the link between DII and PC grade. A case-control study among Mexican men (394 PC cases/794 controls), found, similar to our study, a weak and non-significant suggestion that higher DII scores were correlated with increased PC risk and aggressiveness (p-trend=0.14).[24] In a prospective cohort of 40,161 from the California Men's Health Study (CMHS), a higher DII (3rd Q) was associated with higher risk of high-grade PC, however this association became null in the fourth Q, p-trend=0.74, suggesting a non-linear dose-response.[23] As such, our results and those of the prior study among Mexican men did not reach statistical significance (except DII with supplements on multivariable analysis in our study), these studies found very similar results – trends toward increased risk of high-grade PC with higher DII scores. Again, larger studies or a formal meta-analysis of the published studies are needed to better examine this issue.

Several reasons may explain the small discrepancy among the various studies. First, the DII calculation in the present study was based on 33-food parameters compared to the 31-food parameters used to calculate DII scores in the Italian case-control study.[17] Second, the FFQ used in the Italian study included 78 foods and beverages as well as a range of the most common Italian recipes, whereas our study used a 61 item FFQ [29] of the most common foods consumed in the USA. Third, our study included White and Black men, compared to only White men in the Italian study, and although we did not observe statistically significant differences by race in the association between DII and PC risk, the discrepant results may have been influenced by this racial distribution. The Canadian study used 18-food parameters from their 67-item FFQ to develop the DII score, and while the food items are probably similar to the ones consumed in the U.S., it was limited by only having 72 PC cases which may explain the broad confidence intervals when DII was used as a categorical variable (OR=3.50, 95% CI 1.25–9.80).[20] However, our results are in complete agreement with the Iranian (21-food parameters),[18] French (36-food parameters),[22] and Jamaican (21-food parameters),[19] studies, where a trend in the association was found between higher DII and overall PC risk, though this did not reach statistical significance in our study or any of these latter studies.

Considering that all studies found either significantly increased PC risk with higher DII or non-significant trends in that direction, these results do support the hypothesis that a pro-inflammatory diet, measured by the DII, may play a role in PC risk – especially aggressive PC. The link between inflammation and PC is supported by evidence from studies showing a positive association between higher concentrations of inflammatory biomarkers and

increased risk of PC.[9, 42, 43] Likewise, the use of NSAIDs is associated with a reduced risk of PC.[44] A pro-inflammatory diet may be linked to increased PC risk through components of the metabolic syndrome. We previously found that components of the metabolic syndrome were associated with a higher risk of PC among men undergoing biopsy.[45] A higher DII score also was associated with glucose intolerance,[32] indicating that glucose intolerance and insulin resistance may lead to PC through the growth-promoting effects of the IGF-1/IGF-1R/insulin pathway.[46] Given that previous studies showed Black men are more hyperinsulinemic and insulin resistant when compared to White men,[47, 48] our present results showing that Black men had higher DII scores than White men are in agreement with those data. Taking together this evidence may explain why Black men present with more aggressive PC at diagnosis,[49] even though our study was not sufficiently powered to observe a racial difference in the association between higher DII score and risk of high-grade PC. The only other study that included Black men, found that race modified the association between DII score and high-grade PC. In Black men with high-grade PC the DII score was higher in Q2 and increased fourfold in Q3.[23] As mentioned above, future studies should test whether an anti-inflammatory diet, especially in Black men could reduce PC risk, including high-grade PC.

Strengths of our study include its multiethnic nature, which included 58% Black cases, and the use of a novel DII score to assess the potential inflammatory effect of a Western diet in relation to PC risk. Limitations include the fact that the sample size was not large thus DII quartile numbers were relatively small. Controls were recruited from out-patients seen in a hospital setting. Thus, the diet and comorbidities of these controls may not be representative of the general population. FFQs, including the one we used, may not be optimal to capture the true range of DII and its variability over time, and we cannot exclude the possibility of recall bias. We did not have data on frequency, dose, and duration of supplements used and we merely captured use (yes/no) at the time of study enrollment. However, most cases completed questionnaires prior to the biopsy when they did not know whether they had PC or not minimizing concerns over diet behavior modification bias due to diagnosis. We found black men had higher DII scores and we previously showed in this cohort that black men were more likely to have high-grade PC.[50] While there was no collinearity between DII and race, given our small sample size, we cannot easily distinguish which is driving these effects. However, there was no interaction between race and DII for predicting high-grade PC suggesting high DII is linked with PC independent of race, though more studies in multiracial cohorts are needed. In summary, our findings suggest a pro-inflammatory diet may be associated with increased high-grade PC risk in our case-control study. Future studies are needed to confirm these findings and understand the role of supplements on inflammation and PC risk. If results are confirmed, this would support future studies testing whether a low-inflammatory diet can decrease the risk of high-grade PC, especially among Black men.

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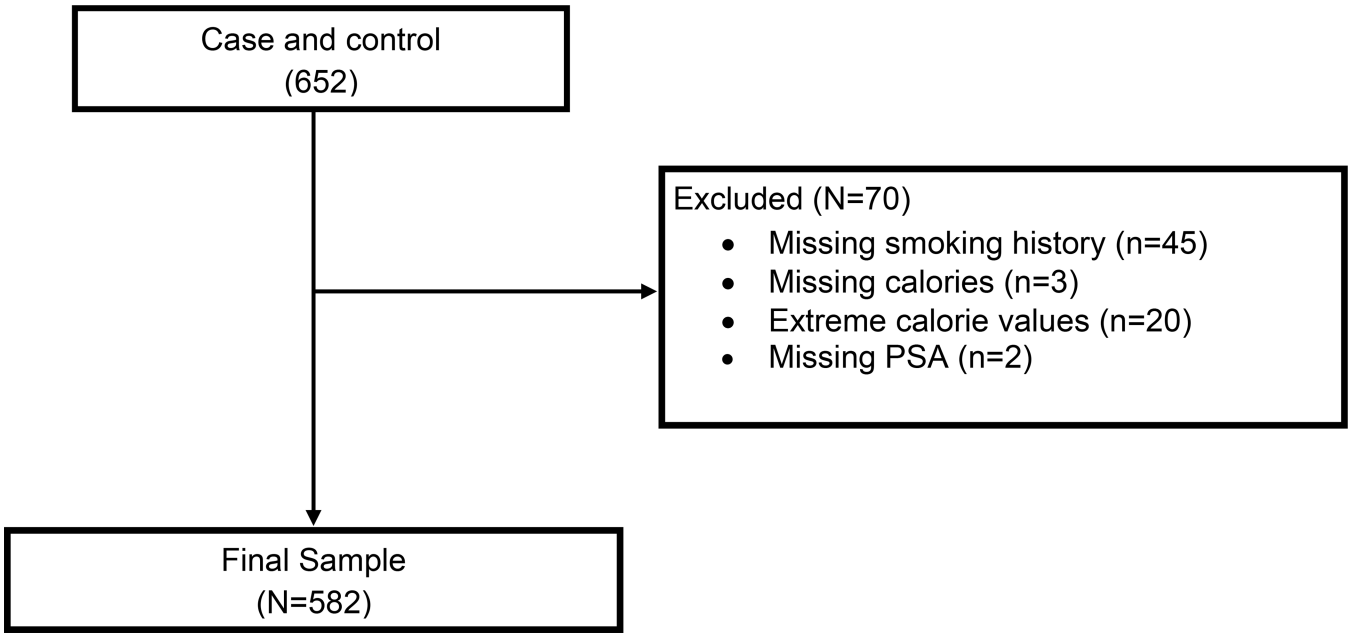

Figure 1:
Consort diagram of final sample used for analysis

Table 1:

Baseline characteristics for biopsy-positive patients (cases) and controls.

	Cases (N=254)	Controls (N=328)	p value
Age			<0.001
Median (IQR)	64 (60, 68)	62 (58,66)	
Race			<0.001
White	106 (42)	231 (70)	
Black	148 (58)	97 (30)	
Daily calorie intake			0.65
Median (IQR)	1599.2(1230.9, 2196.0)	1696.9(1220.1, 2232.7)	
DII with supplements (continuous)			0.15
Median (IQR)	0.8 (−1.7, 2.9)	0.3 (−2.2, 2.6)	
DII with supplements (quartiles)			0.18
Q1	90 (27)	57 (23)	
Q2	84 (25)	61 (24)	
Q3	74 (23)	70 (27)	
Q4	80 (24)	66 (26)	
DII without supplements			0.45
Median (IQR)	1.6 (−0.7, 3.5)	1.2 (−1.3, 3.7)	
DII without supplements (quartiles)			0.37
Q1	92 (28)	55 (22)	
Q2	77 (23)	68 (27)	
Q3	74 (23)	71 (27)	
Q4	85 (26)	60 (24)	
PSA (ng/mL)			
Median (IQR)	6.4 (4.9, 8.6)	0.8 (0.5, 1.5)	<0.001
BMI (kg/m^2)			
Median (IQR)	29.1 (25.8, 32.6)	30.6 (27.1, 33.8)	0.003
Current or former smoker?			0.62
No	80 (32)	97 (30)	
Yes	174 (68)	231 (70)	
Biopsy Grade group			
1	119 (47)	-	
2–5	135 (53)	-	

BMI = body mass index, DII= Dietary Inflammatory Index, PSA = prostate-specific antigen, IQR= Interquartile range.

Table 2:

Assessment of the difference between the distributions of DII with (out) supplement by race (Black vs. White) separately for controls and cases.

	Controls (N=328)			Cases (N=254)		
	Black (N=97)	**White (N=231)**	**p-value[1]**	**Black (N=148)**	**White (N=106)**	**p-value[1]**
DII with Supplement						
Median (IQR)	0.95 (−1.89, 3.87)	−0.04 (−2.48, 2.23)	0.016	1.55 (−0.71, 3.28)	−0.23 (−2.25, 1.61)	<0.001
Mean	0.86	−0.02		1.15	−0.15	
DII without Supplement						
Median	1.54 (−0.72, 4.20)	1.09 (−1.37, 3.46)	0.174*	2.00 (0.30, 3.54)	0.78 (−1.39, 3.12)	0.006
Mean	1.28	0.83		1.59	0.70	

[1] Mann-Whitney U test

* Not statistically significant.

Abbreviation: DII=Dietary Inflammatory Index

Table 3:

Odds ratios and 95% confidence intervals for risk of overall, low-grade, and high-grade PCA relative to no PC based on biopsy-positive patients versus controls.

		Unadjusted		Multivariable*	
	N_1/N_0	OR (95% CI)	p-value	OR (95% CI)	p-value
Overall PC (n=254)					
DII with supplements					
Q1	57/90	Reference	0.18	Reference	0.14
Q2	61/84	1.15 (0.72–1.83)		1.57 (0.93–2.64)	
Q3	70/74	1.49 (0.94–2.38)		1.61 (0.94–2.76)	
Q4	66/80	1.30 (0.82–2.07)		1.57 (0.85–2.88)	
Low-Grade PC (n=119)					
DII with supplements					
Q1	31/90	Reference	0.83	Reference	0.72
Q2	26/84	0.90 (0.49–1.64)		1.23 (0.64–2.35)	
Q3	36/74	1.41 (0.80–2.50)		1.46 (0.77–2.79)	
Q4	26/80	0.94 (0.52–1.72)		1.06 (0.50–2.27)	
High-Grade PC (n=135)					
DII with supplements					
Q1	26/90	Reference	0.06	Reference	0.04
Q2	35/84	1.44 (0.80–2.60)		1.99 (1.05–3.77)	
Q3	34/74	1.59 (0.87–2.89)		1.77 (0.91–3.47)	
Q4	40/80	1.73 (0.97–3.09)		2.23 (1.07–4.65)	
Overall PC (n=254)					
DII without supplements					
Q1	55/92	Reference	0.36	Reference	0.09
Q2	68/77	1.48 (0.93–2.36)		1.45 (0.86–2.45)	
Q3	71/74	1.61 (1.01–2.56)		1.91 (1.07–3.41)	
Q4	60/85	1.18 (0.74–1.89)		1.53 (0.72–3.23)	
Low-Grade PC (n=119)					
DII without supplements					
Q1	26/92	Reference	0.86	Reference	0.47
Q2	34/77	1.56 (0.86–2.83)		1.51 (0.79–2.90)	
Q3	37/74	1.77 (0.98–3.18)		1.96 (0.95–4.03)	
Q4	22/85	0.92 (0.48–1.74)		1.06 (0.40–2.80)	
High-Grade PC (n=135)					
DII without supplements					
Q1	29/92	Reference	0.21	Reference	0.08
Q2	34/77	1.40 (0.78–2.50)		1.39 (0.73–2.63)	

		Unadjusted		Multivariable*	
	N_1/N_0	OR (95% CI)	p-value	OR (95% CI)	p-value
Q3	34/74	1.46 (0.81–2.61)		1.84 (0.91–3.74)	
Q4	38/85	1.42 (0.81–2.50)		2.01 (0.83–4.87)	

Abbreviations: PC: Prostate cancer, OR: Odds ratio; CI: confidence interval

*Adjusted for age, race, BMI, smoking history, and daily caloric intake, Q1, Q2, Q3 and Q4 are quartiles of DII with and without supplements.

§p-value for trend calculated by entering the median value of DII for each quartile of DII into the model as a continuous variable.

N_0: controls; N_1: represents the number of men diagnosed with prostate cancer, low-grade or high-grade prostate cancer, respectively within each quartile of DII (with or without supplement)