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Dietary Patterns and Risk of Gleason Grade progression among men on Active Surveillance for Prostate Cancer: Results from the Canary Prostate Active Surveillance Study

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Abstract

Modifiable lifestyle factors, such as following a healthy dietary pattern may delay or prevent prostate cancer (PCa) progression. However, few studies have evaluated whether following

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Author Disclosures

J.M.S conceived of and designed the analysis, interpreted data, wrote the manuscript, and revised content based on feedback; L.F.N and M.L.N assisted with the study design, interpretation of data and provided critical input for the manuscript; M.L., Y.Z. and K.Z performed data analyses and interpretation; J.D.B, P.R.C, A.D., W.J.E, C.P.F, M.E.G, M.L, F.M.M, T.M.M, A.A.W. and D.W.L. assisted with data collection; D.W.L. had primary responsibility for final content. All authors have read and approved the final manuscript.

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specific dietary patterns after PCa diagnosis impacts risk of disease progression among men with localized PCa managed by active surveillance (AS). 564 men enrolled in the Canary Prostate Active Surveillance Study, a protocol-driven AS study utilizing a pre-specified prostate-specific antigen monitoring and surveillance biopsy regimen, completed a food frequency questionnaire (FFQ) at enrolment and had ≥ 1 surveillance biopsy during follow-up. FFQs were used to evaluate adherence to the Dietary Guidelines for Americans (Healthy Eating index (HEI))-2015, alternative Mediterranean Diet (aMED), and Dietary Approaches to Stop Hypertension (DASH) dietary patterns. Multivariable-adjusted hazards ratios (HRs) and 95% confidence intervals were estimated using Cox proportional hazards models. During a median follow-up of 7.8 years, 237 men experienced an increase in Gleason score on subsequent biopsy (grade reclassification). Higher HEI-2015, aMED or DASH diet scores after diagnosis were not associated with significant reductions in the risk of grade reclassification during AS. However, these dietary patterns have well-established protective effects on chronic diseases and mortality and remain a prudent choice for men with prostate cancer managed by AS.

Keywords

Diet Quality; Prostate Cancer; Epidemiology; Active Surveillance; Healthy Eating Index (HEI) 2015; Alternative Mediterranean Diet (aMED); Dietary Approaches to Stop Hypertension (DASH)

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer and remains the second leading cause of cancer death among men in the United States.[1] Ninety percent of prostate cancers are diagnosed at the localized or regional stage, for which the 5-year survival rate approaches 100%.[2] In recognition of the low-risk nature of localized PCa and the potential risks of overtreatment, Active Surveillance (AS), involving careful monitoring with laboratory, clinical and biopsy assessments, has emerged as a standard of care management option for men with low-risk PCa.[3] Over the last decade the use of AS in the US has increased substantially, with more than half of men with low-risk PCa using AS as initial management.[4-7]

Despite their initial low-risk status, many men with PCa on AS experience adverse grade reclassification and curative intent treatment is recommended. Between 15 and 54% of men on AS experience adverse grade reclassification within 5 years and up to 70% within 10 years.[8] The heterogenous disease course of low-risk prostate cancers underscores the importance of secondary prevention, and there is growing interest in the role of modifiable lifestyle factors, such as diet, that may prevent or delay progression.[9]

An emerging body of evidence suggests that dietary intake after PCa diagnosis may influence disease progression and mortality.[10] However, the majority of these studies have focused on intakes of individual nutrients or foods in relation to biochemical progression or mortality after curative intent treatment. Dietary patterns, which broadly reflect food and nutrient consumption and account for the potential synergistic effects of multiple dietary components[11; 12], might provide additional insight into the role of diet in prostate cancer progression. Prior studies from large observational cohort studies have been inconsistent,

with one reporting no association between adherence to the Mediterranean diet pattern and risk of disease-specific mortality[13], and the other reporting the Western dietary pattern was associated with higher prostate cancer-specific and all-cause mortality[14]. In addition, two prior studies among men on AS reported suggestive, but non-significant lower risks of grade progression among men who consumed diets more closely aligned with the Dietary Guidelines for Americans (Health Eating Index (HEI)-2015) or Mediterranean diet patterns.[15; 16] In the present study, data from the prospective, multi-center Canary Prostate Active Surveillance Study (PASS) were used to investigate whether higher diet quality after PCa diagnosis, measured by adherence to the Dietary Guidelines for Americans (Healthy Eating Index (HEI))-2015, alternative Mediterranean Diet (aMED) and Dietary Approaches to Stop Hypertension (DASH) diet patterns, is associated with decreased risk of grade progression on AS.

Materials and Methods

Data are from the Canary Prostate Active Surveillance Study (PASS), a multicenter prospective cohort of men diagnosed with clinically localized prostate cancer whose treatment plan was AS to manage their prostate cancer.[17] The Canary PASS cohort was established in 2008 and includes 10 clinical sites throughout North America. Under the PASS protocol, prostate-specific antigen (PSA) was measured every 3 months, clinic visits occur every 6 months, and surveillance biopsies are performed 6 to 12 months and 24 months after initial diagnosis, and then every 2 years. Magnetic resonance imaging (MRI) may be performed at the discretion of participating clinicians. At each 6-month clinic visit, clinical and pathologic data are collected. At enrolment in PASS, 5-year PSA and biopsy history including prostate size is collected, and patients provide self-reported race/ethnicity, family history of PCa, and smoking status. In addition, clinic staff measure height and weight to calculate body mass index (BMI) and participants are given a self-administered Food Frequency Questionnaire (FFQ) to complete and return via postage-paid envelope. All men provided written informed consent prior to enrolment in PASS, and study procedures were approved by the local institutional review board for each study site (clinicaltrials.gov NCT000756665).

The analytic sample for this report was drawn from the first 1,000 men enrolled in PASS between August 2008 and October 2013, who were provided the FFQ at study enrolment. Of these, men who enrolled in PASS more than 5 years after diagnosis (n=37), had Gleason Grade Group (GG) 3 disease at enrolment (n=16), or did not have at least one surveillance biopsy after enrolment (n=149) were excluded. Additional exclusion criteria included missing dietary assessment questionnaire (n=224) and reporting extreme energy intake (<800 or >5,000 kcal/day) (n=9), leaving 565 men for these analyses.

Diet Quality Assessment

Measures of diet quality were derived from the FFQ, which was developed by the Nutrition Assessment Shared Resource of the Fred Hutchinson Cancer Research Center, Seattle, Washington.[18] The FFQ asked about frequency of consumption and portion size for 120 composite and single food and beverage items consumed over the prior 3 months. FFQ

responses were converted into estimated daily nutrient and food serving intakes using the Nutrition Data System for Research (NDSR), version v2012 (University of Minnesota, Minneapolis, MN)[19]. To estimate the food group equivalents for each line item on the FFQ, NDSR also links component food items on the FFQ to food items within the MyPyramid Equivalents Database (version 2.0 (US Department of Agriculture)).[20]

Diet quality was measured using the following indices: 1) Healthy Eating Index (HEI)-2015[19], 2) alternative Mediterranean Diet (aMED)[21] and 3) Dietary Approaches to Stop Hypertension (DASH)[22]. The HEI was developed by the US Department of Agriculture (USDA) and National Cancer Institute to assess adherence to the 2015 Dietary Guidelines for Americans[23], which emphasizes foods beneficial for overall health, including fruits and vegetables, whole grains and lean proteins. The aMED score reflects adherence to a Mediterranean dietary pattern, which is abundant in monounsaturated fat, plant proteins, whole grains, and fish; moderate in alcohol; and low in red meat, refined grains, and sweets[24], and the DASH score is based on food and nutrients emphasized (fruits, vegetables, whole grains, low-fat dairy, nuts, seeds and legumes) or minimized (refined grains, red and processed meat, and sodium) in the DASH diet[25]. Index scores are calculated for each participant, with higher scores indicating a higher-quality diet. The components of each diet quality index and criteria for maximum scoring are provided in Supplemental Table 1.

Outcome Assessment

The primary outcome for these analyses is time from enrolment to grade reclassification, defined as any increase in primary or secondary Gleason grade at any surveillance biopsy on AS. Gleason score at re-biopsy was assigned by a pathologist at the local PASS site and abstracted from medical records.

Statistical Analyses

HEI, aMED and DASH scores were categorized into tertiles (low, medium, high) based on the overall study sample distribution. Descriptive statistics were used to characterize the study sample. Differences between tertiles of diet quality indices were evaluated using Wilcoxon sign rank tests for continuous variables and Fisher's tests for categorical variables. Univariate Pearson correlations between index scores were calculated.

Cox proportional hazards models (PH) models were used to estimate covariate-adjusted hazards ratios and 95% confidence intervals for associations between diet quality index and time to reclassification. Person-years of follow-up were calculated from date of enrolment until date of reclassification event (cases) or censor. Participants were censored at the first event of curative-intent treatment, last study contact or 2 years after the last study biopsy; the latter criteria precludes the accrual of time during which grade classification is no longer being assessed. Models were adjusted for Gleason Grade Group (GG 1 (Gleason 3+3) vs GG 2 (Gleason 3+4)) at diagnosis, percentage of cores positive for cancer at diagnosis (calculated as the number of cores positive for cancer divided by the total number of cores collected, continuous), PSA at diagnosis (continuous), and prostate size (continuous). For the small number (n=15) of men who experienced a grade reclassification event prior to enrolment but continued on AS and met all study eligibility criteria, diagnostic clinical

covariate data (PSA, Gleason Grade Group, number of cores positive for cancer, number of cores collected) were updated accordingly. Additional covariates considered include the following: age at diagnosis (continuous), body mass index (BMI) at enrolment (continuous), smoking status (ever vs. never), total energy intake (continuous), time between diagnosis and PASS enrolment (continuous). Adjustment for self-identified race/ethnicity, alcohol intake at enrolment (HEI and DASH only) and family history of prostate cancer (yes vs no/unknown) did not change the results; therefore, these variables were not included in the main analysis. To test for linear trend across tertiles of intake, index scores were modeled as continuous variables. The baseline hazard for each Cox PH model was stratified by study site to account for any site-by-site differences in reclassification rates. Tests of proportionality confirmed that PH assumptions were met.

To explore the potential for non-response bias in our sample, we compared the distribution of covariates between participants who did and did not complete the study FFQ. We applied an inverse probability weighting (IPW) method to account for the non-random subset of men who completed the FFQ.[26] Additional details on IPW methodology are included in the Supplementary Materials. To assess the potential impact of FFQ non-response on associations of diet quality and reclassification, Cox PH models were rerun using the inverse probability weighted dataset.

To test whether associations of diet quality with reclassification risk differed by BMI, we also conducted analyses stratified by BMI (categorized as <25 or ≥25.0 kg/m^2) at enrolment, and Wald chi-square tests were used to test significance of the interaction term of diet quality and BMI. Sensitivity analyses were performed among the subset of men (n=477) who did not experience grade reclassification at the first on-study biopsy (biopsy 1). All analyses were performed using R version 3.3.0, and a two-sided p-value of <0.05 was considered statistically significant.

Results

Across diet quality indices, compared with men with a lower diet diet quality (tertile 1), men with higher diet quality (tertile 3) had lower BMI values, were less likely to be current/former smokers, and were less likely to have diabetes (Table 1). Univariate correlations between the 3 diet quality indices were moderate to strong, ranging from 0.57 to 0.74 (all P<0.05), with the strongest correlation between aMED and DASH. The median number of surveillance biopsies on study, number of PSA per year, time between diagnosis and enrolment and length of follow-up on PASS were similar across tertiles of diet quality score.

Over a median of 7.8 years of PASS follow-up, a total of 237 (42.0%) men experienced grade reclassification. Table 2 gives multivariable-adjusted associations of diet quality score with risk of pathologic reclassification at biopsy on AS. In models adjusted for well-established risk factors for grade reclassification (% cores positive for cancer, PSA, prostate size, Gleason Grade Group), we found slight inverse associations of HEI-2015, aMED and DASH diet quality score with risk of grade reclassification; however, no associations reached statistical significance. The multivariable-adjusted HRs comparing men in the highest to lowest tertile of HEI-2015, aMED and DASH diet score were 0.87 (95%

CI, 0.63, 1.20), 0.92 (95% CI, 0.65, 1.30) and 0.91 (95% CI, 0.65, 1.26) respectively (Table 2). Further adjustment for demographic/lifestyle factors (age at diagnosis, body mass index at enrolment, smoking status, total energy intake, time between diagnosis and PASS enrolment and alcohol intake) did not appreciably impact the associations of diet quality with reclassification (HEI-2015 T3 vs T1: 0.94 (0.67-1.32); aMED T3 vs T1: (0.95 (0.66-1.37); DASH T3 vs T1: 0.90 (0.64-1.27). Additional analyses were conducted to address potential bias due to FFQ non-response. Twenty-nine percent of PASS participants did not return the FFQ, and non-responders tended to be younger, less compliant with PSA screening, had a larger prostate and a higher BMI. (Supplemental Table 2) After applying IPW methods, we observed no appreciable differences in the associations between diet quality indices and grade reclassification (Table 2).

Table 3 gives multivariable-adjusted associations between diet quality and grade reclassification stratified by BMI at enrolment. There was no evidence of a significant interaction between BMI and HEI-2015 or DASH diet score. Among men with BMI ≥ 25.0 kg/m^2, the highest compared to lowest tertile of aMED diet score was associated with a non-significant 17% lower risk of grade reclassification ($P_{interaction}$=0.16).

Discussion

In this analysis from a prospective multi-institutional cohort of men with localized PCa being managed by AS, we found little evidence of an association between diet quality after diagnosis and risk of grade reclassification. While higher Healthy Eating Index-2015, alternative Mediterranean and DASH dietary pattern scores were associated with a slight inverse risk of grade reclassification, no associations reached statistical significance.

Several studies have reported inverse associations between high diet quality with prostate cancer risk[13; 27-30]; however, data on diet quality after diagnosis and prostate cancer outcomes remains limited. In the Physicians Health Study, a “Western” dietary pattern (characterized by high intakes of red meats, high-fat dairy and refined grains) increased the risk of prostate cancer specific death, whereas a “Prudent” dietary pattern (identified by principle component analysis and characterized by high intakes of vegetables, fruits, fish, legumes and whole grains) after PCa diagnosis was associated with a reduced risk of overall death, (HR Q4 vs 1: 2.53, 95% CI: 1.00-6.42, p-trend=0.01; HR Q4 vs 1: 0.64, 95% CI: 0.44-0.93, p-trend=0.02, respectively).[14] In contrast, in the Health Professionals Follow-up Study, higher adherence post-diagnosis to the traditional Mediterranean Diet, which has many similarities to the “Prudent” diet, was not associated with prostate cancer specific death.[13] While these studies provide limited evidence in support of a role for diet quality in prostate cancer progression, the majority of prostate cancers in these cohorts pre-date the AS era and underwent curative intent treatment; therefore, the relevance of findings from these studies to AS populations is unclear.

To date, few studies have specifically evaluated post-diagnosis diet among men with localized PCa managed by active surveillance.[16; 31] Two studies from a single-site observational cohort at MD Anderson reported that higher Mediterranean Diet and HEI-2015 scores were associated with marginally significant reductions in risk of Gleason

score upgrading during AS (Med HR T3 vs T1: 0.67, 95% CI: 0.36-1.25, p_{trend}=0.05; and HEI-2015 HR T3 vs T1: 0.59, 95% CI: 0.32-1.08, p_{trend}=0.06).[16] However, a recent phase-3 randomized trial among PCa patients on AS reported inconsistent results. While not targeting a dietary pattern specifically, this 1-year behavioral intervention promoted high fruit and vegetable intake (≥ 7 servings/day), foods which contribute both directly and indirectly to up to 50% of the scoring for the dietary patterns we evaluated. The intervention yielded statistically significant increases in fruit/vegetable consumption; however, no significant differences were found in time to PCa progression (defined as PSA≥10 ng/mL, PSA doubling time of <3 years, increase in tumor volume or grade on follow-up biopsy) between the intervention and control arms (HR: 0.97, 95% CI: 0.76, 1.25).[31]

Although the MD Anderson and PASS cohorts share important features, such as the standardized collection of biopsies at protocol-directed time-points, which minimizes the potential for detection bias; there are several analytic differences which could contribute to the conflicting results. First, the reclassification event rate differed substantially between the MD Anderson (n=76; 18.5%) and PASS (n=237; 41.9%) analyses, likely related to differences in the study-specific definitions of reclassification. In the MD Anderson analyses, reclassification was defined as an increase in GG following the confirmatory (first AS) biopsy, whereas for PASS, an increase in GG at any follow-up biopsy was included as a reclassification event. To provide a more direct comparison with these prior studies, we conducted a sensitivity analysis among the subset of men (n=477) who did not experience grade reclassification at the first on-study biopsy (biopsy 1); however, no substantial differences in the associations of diet pattern scores with grade reclassification were noted. The inconsistent results may also be a related to differences in the Mediterranean diet pattern scoring. Compared to the original Mediterranean diet pattern score evaluated by Gregg et al., the alternative scale evaluated in PASS was adapted for use in a US population[21] and excludes potato products from the vegetable group, separates fruit and nuts into 2 groups, eliminates the dairy group, includes only red and processed meats for the meat group, and assigns 1 point for alcohol intake between 5 and 15 grams per day (approximately 1 drink per day), as opposed to 0 to 13 drinks per week (approximately 2 drinks per day). Furthermore, there were substantial differences in length of follow-up (a median of 3.0 years in the MD Anderson cohort vs 7.8 years in PASS), and modest differences in covariate adjustment in models, and in the HEI-2015 diet index cut-points (MD Anderson: 34.8-63.3, 63.3-72.7, 72.9-95.1 vs. PASS:43.5-65.7, 65.8-74.5, 74.692.7).

Men with low-risk PCa on AS have an excellent cancer-specific prognosis. [32] However, other chronic diseases including cardiovascular disease and other cancers, remain primary causes of morbidity among these men.[33] Even though our results do not support a protective association for HEI-2015, aMED or DASH dietary patterns in terms of prostate cancer progression, adherence to these dietary patterns may offer protection from other chronic diseases. HEI-2015, aMED or DASH dietary patterns have well-established protective effects on cardiovascular disease and overall and cancer mortality.[34-38] In addition, although the “Prudent” and aMED diet patterns were not associated with PCa-specific mortality, these patterns were associated with improved overall survival among PCa patients.[13; 14] Thus, it may be advisable to encourage prostate cancer patients on AS to adopt a healthy dietary pattern.

Strengths of this study include the long follow-up (median of 7.8 years on PASS) and the use of a standardized follow-up protocol across all clinical sites. In addition, the intentionally broad eligibility criteria of the PASS cohort, which includes Gleason Grade Group 1 and 2 disease, and multicenter design increases the generalizability of these results to the current population of men eligible for and electing to undergo AS. Some limitations should be considered when interpreting our findings. Our study is relatively small, lacks information on potential confounders (i.e. physical activity) and is subject to non-differential measurement error inherent in all dietary assessment methods.[39] In addition, the lack of heterogeneity in diet pattern scores, in particular for HEI-2015, may have impacted our ability to detect associations. Lastly, 28% of participants did not return the FFQ, suggesting the potential for non-response bias. Nevertheless, analyses addressing non-response yielded comparable results.

In conclusion, these results indicate that higher adherence to HEI-2010, aMED or DASH dietary patterns many not play an important role in the progression of low-risk prostate cancer managed by active surveillance. While our results do not support a protective effect of high-quality dietary patterns in terms of Gleason Grade progression, these dietary patterns have well-established protective effects on many chronic diseases and overall mortality and remain a prudent choice for this population of men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline demographic and clinical characteristics of 565 Canary Prostate Active Surveillance Study (PASS) participants with diet data.

	Health Eating Index HEI-(2015) Score			Alternative Mediterranean Diet Score			DASH Diet Score		
Diet Quality Index, range	**43.5 - 65.9**	**66.0 – 74.5**	**74.5 - 92.7**	**0 - 3**	**4-5**	**6 - 9**	**12 - 22**	**23 - 27**	**28 - 37**
n	188	188	188	205	211	148	195	186	183
Age, years, median [IQR]	64 [60,67]	64 [60, 67]	64 [59, 67]	64 [60, 67]	63 [58, 68]	63 [57, 66]	63 [58, 67]	64 [59, 68]	63 [58, 67]
BMI, kg/m^2, median [IQR]	28.2 [25.6,31.0]	27.2 [24.9, 29.8]	25.8 [23.7, 28.1]	27.3 [24.8, 30.3]	27.2 [25.2, 29.8]	26.1 [24.0, 28.8]	27.9 [25.6, 31.1]	26.9 [24.8, 29.4]	26.1 [24.2, 28.6]
Race, n (%)									
Black	9 (5)	10 (5)	7 (4)	12 (6)	9 (4)	5 (3)	15 (8)	3 (1)	8 (5)
White	168 (89)	176 (92)	171 (91)	182 (88)	115 (55)	193 (93)	168 (86)	175 (94)	169 (92)
Other	12 (6)	5 (3)	10 (5)	12 (6)	52 (25)	6 (4)	12 (6)	9 (5)	6 (3)
Family history of Prostate Cancer, n (%)									
Yes	46 (24)	46 (24)	51 (27)	47 (23)	56 (27)	40 (27)	52 (27)	40 (21)	51 (28)
No	131 (69)	131 (70)	123 (65)	145 (70)	140 (66)	100 (68)	129 (66)	132 (71)	124 (68)
Unknown	12 (6)	11 (6)	14 (8)	14 (7)	15 (7)	8 (5)	14 (7)	15 (8)	8 (4)
Smoking status, n (%)									
Ever	94(50)	117 (42)	57 (36)	99 (48)	88 (41)	54 (36)	104 (48)	80 (42)	78 (38)
Never	95 (50)	108 (58)	121 (64)	107 (52)	123 (59)	97 (64)	101 (52)	107 (58)	116 (63)
Diabetes, n (%)									
Yes	19 (10)	12 (6)	7 (4)	20 (8)	16 (8)	2 (1)	17 (8)	15 (8)	6 (3)
No	189 (92)	176 (94)	203 (97)	186 (91)	195 (92)	146 (99)	198 (92)	172 (92)	200 (97)
Energy Intake, kcal, median [IQR]	2132 [1480, 2727]	2,126 [1724, 2658]	2021 [1628, 2540]	1820 [1364, 2310]	2,172 [1,757, 2,672]	2400 [1930, 2876]	2037 [1534, 2632]	2,078 [1599, 2,616]	2172 [1757, 2656]
Alcohol, grams, median [IQR]	2.9 [0.04, 16.1]	11.1 [2.0, 22.2]	10.8 [2.0, 23.9]	3.8 [0, 20.0]	10.0 [0.9, 20.9]	9.3 [2.8, 20.2]	7.5 [0.7, 21.5]	9.2 [1.3, 21.7]	8.3 [1.0, 19.3]
Clinical Characteristics									
Prostate size, cc, median [IQR]	38.4 [28.2, 52.5]	42.3 [28.9,57.8]	39.6 [28.3, 57.0]	38.3 [28.7, 55.7]	42.2 [27.9, 59.0]	39.2 [28.8, 48.5]	38.0 [28.3, 53.8]	44.4 [29.8, 59.2]	40.0 [27.5, 52.8]

	Health Eating Index HEI-(2015) Score			Alternative Mediterranean Diet Score			DASH Diet Score		
Diet Quality Index, range	**43.5 - 65.9**	**66.0 – 74.5**	**74.5 - 92.7**	**0 - 3**	**4-5**	**6 - 9**	**12 - 22**	**23 - 27**	**28 - 37**
% of cores positive for cancer, mean (SD)									
	14.5 (9.5)	14.1 (9.1)	14.1 (8.6)	14.5 (9.4)	14.0 (9.0)	14.3 (8.9)	14.4 (9.8)	14.7 (9.3)	13.6 (7.9)
PSA, median [IQR]	4.7 [3.5, 5.9]	4.7 [3.4, 6.3]	4.5 [3.5, 6.0]	4.8 [3.6, 6.3]	4.6 [3.6, 6.1]	4.5 [3.2, 5.7]	4.8 [3.6, 6.2]	4.5 [3.5, 6.0]	4.6 [3.2, 6.0]
Length of PASS follow-up, yrs, median [IQR]									
	7.6 [6.3, 9.3]	7.7 [6.6, 9.5]	8.3 [6.6, 9.9]	7.8 [6.7, 9.4]	8.1 [6.4, 9.8]	7.7 [6.5, 9.5]	7.9 [6.4, 9.4]	7.7 [6.5, 9.4]	8.1 [6.4, 9.8]
Time between diagnosis and enrollment, yrs, median [IQR]									
	0.6 [0.3, 1.2]	0.6 [0.4, 1.3]	0.6 [0.4, 1.3]	0.6 [0.3, 1.1]	0.6 [0.4, 1.4]	0.7 [0.4, 1.5]	0.6 [0.3, 1.2]	0.6 [0.3, 1.3]	0.6 [0.4, 1.4]
Gleason Grade Group									
GG1	168 (90)	173 (92)	174 (93)	189 (92)	190 (90)	136 (93)	180 (93)	168 (90)	167 (92)
GG2	19 (10)	15 (8)	13 (7)	16 (8)	20 (10)	11 (8)	14 (7)	18 (10)	15 (8)
Clinical T Stage, n (%)									
T1	166 (88)	171 (91)	163 (87)	184 (89)	187 (89)	129 (87)	176 (90)	165 (88)	159 (87)
T2	19 (10)	17 (9)	25 (13)	22 (11)	24 (11)	19 (13)	19 (10)	22 (12)	24 (13)

Table 2.

Associations of diet index scores with risk of prostate cancer grade reclassification during Active Surveillance

	Health Eating Index HEI-(2015) Score					
	Low: (43.5-65.7)	**Medium: (65.8-74.5)**	**High: (74.6-92.7)**	***P*-trend**	**Continuous Model[1]**	***P***
Number of events	87	70	80			
HR[2] (95% CI)	1.00	0.81 (0.58, 1.13)	0.87 (0.63, 1.20)	0.15	0.92 (0.80, 1.06)	0.23
HR[2] (95% CI) – IPW[3] adjusted	1.00	0.80 (0.57, 1.13)	0.84 (0.60, 1.16)	0.12	0.92 (0.80, 1.05)	0.22
	Alternative Mediterranean Diet Score					
	Low: (0-3)	**Medium: (4-5)**	**High: (6-9)**	***P*-trend**	**Continuous Model[1]**	***P***
Number of events	92	84	61			
HR[2] (95% CI)	1.00	1.02 (0.75, 1.39)	0.92 (0.65, 1.30)	0.27	0.97 (0.85, 1.12)	0.71
HR[2] (95% CI) – IPW[3] adjusted	1.00	1.03 (0.75, 1.41)	0.86 (0.60, 1.24)	0.14	0.96 (0.83, 1.10)	0.56
	DASH Diet Score					
	Low: (12-22)	**Medium: (23-27)**	**High: (28-37)**	***P*-trend**	**Continuous Model[1]**	***P***
Number of events	91	75	81			
HR[2] (95% CI)	1.00	0.95 (0.69, 1.30)	0.91 (0.65, 1.26)	0.15	0.92 (0.80, 1.06)	0.25
HR[2] (95% CI) – IPW[3] adjusted	1.00	0.91 (0.66, 1.26)	0.89 (0.63, 1.26)	0.14	0.91 (0.79, 1.06)	0.24

[1]Per standard deviation increase in diet index score

[2]Adjusted for PSA, Gleason Grade Group, percentage of cores positive for cancer, prostate size

[3]IPW=Inverse Probability Weighting

Table 3.

Associations of diet index scores with risk of prostate cancer grade reclassification during Active Surveillance, stratified by Body Mass Index

		Health Eating Index HEI-(2015) Score					
		Low: (43.5-65.7)	**Medium: (65.8-74.5)**	**High: (74.6-92.7)**	***P*-trend**	**Continuous Model[1]**	***P***
BMI<25 kg/m^2	Number of events	16	18	27			
	HR (95% CI)	1.00	0.90 (0.42, 1.94)	0.83 (0.39, 1.73)	0.52	0.91 (0.68, 1.20)	0.49
BMI≥25.0 kg/m^2	Number of events	71	52	53			
	HR (95% CI)	1.00	0.76 (0.52, 1.10)	0.89 (0.61, 1.30)	0.30	0.92 (0.78, 1.09)	0.34
		Mediterranean Diet Score					
		Low: (0-3)	**Medium: (4-5)**	**High: (6-9)**	***P*-trend**	**Continuous Model[1]**	***P***
BMI<25 kg/m^2	Number of events	21	17	23			
	HR (95% CI)	1.00	1.17 (0.57, 2.40)	1.14 (0.59, 2.23)	0.74	0.97 (0.75, 1.26)	0.83
BMI≥25.0 kg/m^2	Number of events	71	67	38			
	HR (95% CI)	1.00	0.94 (0.66, 1.33)	0.83 (0.54, 1.27)	0.15	0.98 (0.83, 1.03)	0.77
		DASH Diet Score					
		Low: (12-22)	**Medium: (23-27)**	**High: (28-37)**	***P*-trend**	**Continuous Model[1]**	***P***
BMI<25 kg/m^2	Number of events	17	20	24			
	HR (95% CI)	1.00	1.02 (0.49, 2.14)	1.08 (0.53, 2.22)	0.78	0.94 (0.69, 1.27)	0.69
BMI≥25.0 kg/m^2	Number of events	74	55	47			
	HR (95% CI)	1.00	0.94 (0.65, 1.38)	0.85 (0.58, 1.26)	0.18	0.91 (0.77, 1.07)	0.26

[1] Per standard deviation increase in diet index score

[2] Adjusted for PSA, Gleason Grade Group, percentage of cores positive for cancer, prostate size