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Post-diagnostic Inflammatory, Hyperinsulinemic, and Insulin Resistant Diets and Lifestyles and the Risk of Prostate Cancer Progression and Mortality

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Abstract

Background: Inflammatory and insulin pathways have been linked to prostate cancer (PC); post-diagnostic behaviors activating these pathways may lead to poor outcomes. The empirical dietary inflammation pattern (EDIP), indices for hyperinsulinemia (EDIH) and insulin resistance (EDIR), and associated lifestyle indices (ELIH, ELIR) predict biomarkers of inflammation (EDIP: IL-6, TNFaR2, CRP) and insulin secretion (EDIH/ELIH: c-peptide; EDIR/ELIR: TAG:HDL) from whole foods and behaviors.

Methods: Associations of these indices with time to PC progression (primary, n=2,056) and PC-specific mortality (PCSM; secondary, n=2,447) were estimated among men diagnosed with non-metastatic PC in the CaPSURE cohort diet and lifestyle sub-study. Because the true (versus clinically-documented) date of progression is unobserved, we used parametric (Weibull) survival models to accommodate interval-censoring and estimated adjusted hazard ratios (HR) and 95% confidence intervals (CI) for PC progression per 1-standard deviation increase in index. Cox proportional hazards models were used to estimate PCSM associations.

Results: During a median (IQR) 6.4 years (IQR:1.3, 12.7), 192 progression and 73 PCSM events were observed. Inflammatory (EDIP: HR=1.27, CI: 1.17-1.37), hyperinsulinemic (EDIH: HR=1.24, CI: 1.05-1.46. ELIH: HR=1.34, CI:1.17-1.54), and insulin resistant (EDIR: HR=1.22,

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CI: 1.00-1.48. ELIR: HR=1.36, CI:1.12-1.64) indices were positively associated with risk of PC progression. There was no evidence of associations between the indices and PCSM.

Conclusions: Both inflammatory and insulinemic dietary and lifestyle patterns are associated with risk of PC progression.

Impact: For men with PC, consuming dietary patterns that limit chronic systemic inflammation and insulin hypersecretion may improve survivorship, especially when coupled with active lifestyle and healthy body weight.

Keywords

prostate cancer survivorship; modifiable behaviors; mechanisms; cohort study

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer among men in the United States.[1] Over the past decade, research has identified various dietary and lifestyle factors associated with survival following prostate cancer diagnosis.[2] However, much of the evidence regarding diet in particular remains mixed, leading to uncertainty about the role these factors play in improving outcomes following a diagnosis. Many past studies have examined single dietary factors in isolation, which does not adequately represent the combined impact of dietary intake on biological responses or the complex interactions in whole diets.[3,4] Therefore, it is important to examine dietary patterns to try to understand diet-prostate cancer relationships.

Inflammation and insulin pathways have been linked to cancer development and progression,[5] including in the setting of prostate cancer.[6–12] Post-diagnostic behaviors that over-activate these pathways may therefore lead to poorer prostate cancer outcomes. The empirically-derived inflammatory, hyperinsulinemic, and insulin resistance dietary indices – calculated from food frequency questionnaire (FFQ) data – and the associated lifestyle indices provide an opportunity to study the role of diet- and lifestyle-related inflammation- and insulin- promoting behaviors in prostate cancer outcomes.[13,14] All five indices were developed in the Nurses' Health Study (NHS) and validated in both the NHS-II and the Health Professionals Follow-up Study (HPFS).[13,14] These novel indices have been studied in relation to risk of diabetes,[15] colorectal cancer (onset and progression),[16,17] pancreatic cancer,[18] hepatocellular carcinoma,[19] and prostate cancer (among previously healthy men);[20] however, they have not been examined in men diagnosed with prostate cancer. Because they predict plasma concentrations of circulating markers of inflammation (interleukin-6, C-reactive protein, and tumor necrosis factor α receptor 2)[13], hyperinsulinemia (C-peptide),[14] and insulin resistance (triacylglycerol to high density lipoprotein cholesterol; TAG:HDL)[14], the indices allow for the measurement of the inflammatory and insulinemic potential of whole diets and associated lifestyles without the necessity for biomarker data.

Here, we used these indices to examine associations between the inflammatory and insulinemic potentials of dietary patterns and lifestyle habits after a prostate cancer diagnosis and the risk of disease progression (primary outcome) and disease-specific

mortality (secondary outcome) among men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) cohort. Given the role that increased adiposity may play in activating these pathways,[5,21] we also examined whether obesity modified associations with the dietary indices.

METHODS

Study Sample.

CaPSURE is a longitudinal observational cohort of 15,310 men with biopsy-proven prostate cancer. Participants were enrolled at 43 urology practices across the United States starting in 1999. Data were collected on diagnostic and other clinical features, treatments, and clinical follow-up. Additional details of the CaPSURE cohort have been previously reported.[22] All participants provided written informed consent, and the study was conducted in accordance with the Belmont Report and the U.S. Common Rule under local Institutional Review Board approval.

The CaPSURE Diet and Lifestyle (CDL) sub-study – consisting of a comprehensive lifestyle questionnaire and full-length food frequency questionnaire (FFQ) – was administered at three time points between 2004-2016; a total of 2,891 men participated in at least one administration. For the subset of men who participated in more than one administration (n=443), only the first administration (closest to diagnosis date) was used. Men with a last clinical follow-up (n=160) or documented progression (n=391) prior to completion of their first CDL questionnaire were excluded. Those with unknown or extreme caloric intake (<800 kcal/day or >4200 kcal/day; n=153) and/or missing ≥70 FFQ items (n=20) were also excluded, consistent with the recommended approach to address implausible energy intakes.[23–25] Finally, men with undocumented or unknown clinical T-stage (n=100) or T-stage >T3a (n=8) and those with death from an unknown cause (n=3) were excluded, resulting in a sample size of 2,056 men with non-metastatic disease.

Diet and Lifestyle Questionnaire.

We collected data on education, family history of prostate cancer, smoking history, medical history, supplement use, and height and weight (used to calculate body mass index [BMI]) via questionnaire. Self-reported dietary intake was collected via a validated[23,26–28] semiquantitative FFQ that asked about average consumption of approximately 140 foods/beverages over the past year. Participants reported how often over the prior year they had consumed a specified portion size of each of the items. They could choose from 9 frequency options ranging from never or less than one serving per month to six or more servings per day.

Physical activity was assessed via a validated physical activity questionnaire developed primarily to capture leisure-time physical activity.[29] Participants were asked to report the average weekly time spent doing various aerobic and resistance exercises. Participants could choose from 11 frequency options ranging from 0 minutes to 11 hours per week. A metabolic equivalent of task (MET) value was assigned to each activity based on the energy required by that activity relative to the resting metabolic rate.[30] MET-hours per week were

calculated by multiplying the MET value for an activity by the reported time per week spent doing that activity.

Inflammatory and Insulinemic Potential of Whole Diets.

Development and validation of the empirical dietary inflammatory pattern (EDIP), empirical dietary index for hyperinsulinemia (EDIH), and empirical dietary index for insulin resistance (EDIR) have been detailed previously.[13,14] Briefly, each index was developed in the NHS and subsequently validated in both the NHS-II and HPFS cohorts. Blood samples taken at the beginning of each cohort were used (EDIP development specified samples were only taken in participants free of cancer, diabetes, heart disease, or stroke diagnosis). Diets were measured via FFQs (similar to the FFQ administered in CaPSURE) based on 39 pre-defined food groups that were updated at regular intervals in each cohort. FFQs completed closest to the date of blood draw were used for development and validation of each index. The EDIP was created using reduced-rank regression and stepwise linear regression to identify a dietary pattern that was predictive of three plasma inflammatory markers (interleukin-6, C-reactive protein, and tumor necrosis factor α receptor 2), resulting in the inclusion of 9 pro-inflammatory (red meat, processed meat, organ meat, other fish, tomatoes, other vegetables, refined grains, low-energy beverages, and high-energy beverages) and 9 anti-inflammatory (coffee, tea, fruit juice, wine, beer, leafy green vegetables, dark yellow vegetables, snacks, and pizza) food groups. Multivariable models found the EDIP was significantly associated with all three inflammatory biomarkers, with significant linear trends for each biomarker across quintile of the EDIP observed.[13] These results were replicated in validation studies, which also found significant associations with adiponectin, a marker of overall inflammation, which was notably not used in the development of the EDIP.[13]

Using a similar method, the EDIH and EDIR were created by identifying dietary patterns that were most predictive of plasma C-peptide and TAG:HDL, respectively. Although similar metrics, hyperinsulinemia is a consequence of prolonged insulin resistance[5] due to diminished cellular response to insulin, resulting in additional insulin secretion and subsequently high levels of insulin relative to glucose. The EDIH included 13 pro-insulin secretion (red meat, processed meat, other fish, poultry, eggs, margarine, butter, cream soups, low-fat dairy, french fries, tomatoes, high-energy beverages, low-energy beverages) and 5 anti-insulin secretion (coffee, wine, high fat dairy, leafy green vegetables, whole fruit) food groups. The EDIR included 10 pro-insulin resistance (red meat, processed meat, other fish, tomatoes, cream soups, other vegetables, refined grains, margarine, fruit juice, and low-energy beverages) and 8 anti-insulin resistance (coffee, wine, liquor, beer, high fat dairy, nuts, leafy green vegetables, and dark yellow vegetables) food groups. Multivariable models found the EDIH and EDIR were significantly associated with C-peptide and TAG:HDL biomarkers, with the results replicated in validation studies.[14]

The resulting EDIP, EDIH, and EDIR are weighted sums of 18 index-specific food groups (some overlapping), with higher indices reflecting diets with greater inflammatory (EDIP) or insulinemic (EDIH, EDIR) potential. A detailed list of the specific food items included in

each food group for each of these indices can be found in Supplemental Table S1. Weights are available in the original publications describing the creation of the indices.[13,14]

We also considered how two related indices – the empirical lifestyle index for hyperinsulinemia (ELIH) and the empirical lifestyle index for insulin resistance (ELIR), developed using the same methodology as the EDIH and the EDIR – related to prostate cancer outcomes. A lifestyle index for inflammation has not yet been created. Both lifestyle indices included BMI and physical activity in addition to dietary factors (Supplemental Table S1). Details of their development and validation, as well as the weights needed to calculate the indices, are available in the original publication describing the creation and validation of these indices.[14] Multivariable models found the ELIH and ELIR were significantly associated with C-peptide and TAG:HDL biomarkers, with the results replicated in validation studies.[14]

Primary Outcome.

In this cohort of men with non-metastatic prostate cancer at diagnosis, the primary outcome was time to prostate cancer progression. Progression was defined as biochemical recurrence, secondary treatment, bone metastases, or death attributed to prostate cancer (prostate cancer-specific mortality; PCSM). Biochemical recurrence was defined as two consecutive prostate-specific antigen (PSA) readings ≥0.2 ng/mL after radical prostatectomy or two consecutive PSA levels at least 2.0 ng/mL greater than the post-radiation nadir following radiation therapy.[31] The date of recurrence was recorded as the date of the second elevated PSA. Secondary treatment was defined as any treatment started ≥6 months following completion of primary treatment. Bone metastases were attributed to prostate cancer if a urologist reported prostate cancer progression to bone or advancement to TNM stage M1b, the patient had a positive bone scan, or the patient underwent radiation to treat bone metastases. Cause of death was determined by the registry data coordinating center and through confirmation by either the vital statistics official death certificate from the state in which the death occurred or by the National Center for Health Statistics National Death Index. Deaths were attributed to prostate cancer if the death certificate included ICD-9 code 185 [(metastatic) malignant neoplasm of prostate] as the primary or secondary cause of death. For men with multiple progression events, the earliest event date was recorded as the date of progression.

Time to progression was measured from the date of completion of the first questionnaire to the date of progression. However, the exact date of progression is unlikely to have occurred on the date of the clinic visit at which it was recorded. To account for this uncertainty, we used an interval rather than a precise date of progression. For men with documented biochemical recurrence, secondary treatment, or bone metastases, the censoring interval was bound by the last normal clinical visit (left limit) and the first clinic visit documenting evidence of progression (right limit). For men with only a progression event of PCSM, the left and right limit were both date of death. Men without documented progression were censored at their last date of follow-up or death (other cause); thus, the right limit was undefined (i.e., censored). Clinical follow-up was last consistently assessed across all CaPSURE sites on January 31, 2019. The 26 men who had a last known clinical follow-up date beyond this date were administratively censored on January 31, 2019.

Statistical Analysis.

Pearson's r was used to report correlations between each of the 5 indices. Parametric survival models with a Weibull distribution were used to accommodate interval censoring. We fit survival models using both continuous indices [per 1-standard deviation (SD) increase in index] and cohort-specific quintiles. All models were clustered by CaPSURE clinical site, with robust standard errors used to calculate confidence intervals (CI). Simple models were adjusted for age at diagnosis (continuous) and time between diagnosis and first questionnaire (continuous). Fully adjusted models additionally adjusted for T-stage (T1, T2, T3a), Gleason score (<7, 7, >7), and PSA (≤6ng/mL, >6 to 10ng/mL, >10ng/mL) at diagnosis; primary treatment (radical prostatectomy, radiation, hormonal therapy, watchful waiting/active surveillance, other); self-reported race (white, other); total energy intake (continuous, kcal/day); smoking status (current, former, never); family history of prostate cancer in a brother or father (yes/no); total alcohol intake (continuous, servings/day); use of supplements (multivitamins, calcium, vitamin E, or selenium; yes, no); BMI (continuous; models for dietary indices only); and physical activity (continuous, MET-hours/week; models for dietary indices only). We further considered adjustment for height, household income, education, intake of fatty fish and cruciferous vegetables, walking pace, and history of diabetes or heart disease, but estimates were qualitatively unchanged, so these variables were not included in the final models. We examined the goodness of fit of survival models using plots of Cox-Snell residuals. Fully adjusted models were also run using exponential distributions, which produced Cox-Snell residual plots that demonstrated poorer fit than Weibull models; thus, Weibull models were used.

Interaction.

We assessed interactions between each of the dietary indices (EDIP, EDIH, EDIR) and obesity in two ways. First, we created a cross product between each of the indices (continuous) and BMI (<30 vs ≥30kg/m^2). We then used likelihood ratio tests based on models with and without the interaction terms to look for statistically significant multiplicative interactions. To assess additive interaction, we used the BMI thresholds (<30 vs ≥30kg/m^2) and a dichotomized version of each index (above and below median) to create a 4-level variable (high index-high BMI, high index-low BMI, low index-high BMI, low index-low BMI) and added it to the fully adjusted model. Low index/low BMI was used as the referent and HR estimates were used to calculate the relative excess risk due to interaction (RERI).[32,33] The delta method was used to calculate CI that indicated whether RERI results were different from zero (RERI ≠ 0 is evidence of additive interaction).[34]

We evaluated PCSM as our secondary outcome given the small number of PCSM events (n=73) in this cohort of men initially diagnosed with non-metastatic disease. For these analyses, we utilized Cox proportional hazards models rather than parametric survival models because date of death was known. Men who were originally excluded due to documented progression prior to completion of the questionnaire were included in these secondary analyses (as death could not occur prior to completing the questionnaire), resulting in a sample size of 2,447 men. Proportional hazards assumptions were assessed graphically by plotting the scaled Schoenfeld residuals against follow-up time.

Additional Analyses.

We were interested in understanding how deaths due to causes other than prostate cancer (i.e., competing risks) may have impacted our primary results. Methods to address competing risks in the presence of interval censoring are not readily available or accessible. Thus, we ran Cox proportional hazards analyses on our fully adjusted models of progression and compared these results to Fine-Gray analyses accounting for other deaths as a competing risk.[35]

Although there was no missingness for any of the indices, missingness in covariates resulted in a loss of events in our fully adjusted models (n=17). To understand the impact of this missingness on our primary results, we performed a sensitivity analysis utilizing multiple imputation to handle missing data.[36] We performed multiple imputation via chained equations using the *chained* command in Stata to first generate 25 imputed datasets. We then fit survival models across all 25 imputed datasets and pooled the results using Rubin's Rules.[37] Our imputed model included all variables without missingness (EDIP, EDIH, ELIH, EDIR, ELIR, BMI, physical activity, CaPSURE clinical site, age at diagnosis, vital status, total energy intake, days in follow-up, race, clinical T stage, and family history of prostate cancer) and variables with incomplete values (diagnostic PSA and Gleason score, smoking status, supplement use, total alcohol intake, and primary treatment).

All statistical analyses were performed using Stata version 17 (StataCorp, College Station, TX). A two-sided alpha level of 0.05 was used to assess statistical significance.

Data Availability.

Data can be made available on request.

RESULTS

Participant characteristics by quintile of the inflammatory and insulinemic dietary and lifestyle indices are shown in Tables 1–2. The participants had a mean (SD) age of 64.4 (7.9) years at diagnosis, and most (n=1,953; 95%) identified as white race. These characteristics were similar to the larger CaPSURE cohort (mean age: 66.0 (8.6) years; 86% identified as white race). Characteristics were fairly balanced across quintiles of each index, although men consuming more inflammatory and insulinemic diets tended to have higher BMI and lower levels of physical activity. This was also true for men with more insulinemic lifestyles, with a more pronounced increase in BMI and decrease in physical activity, as expected (both are components of these indices). Correlations between the indices are shown in Supplemental Table S2.

During a median follow-up of 6.4 years (IQR: 1.3, 12.7) after completion of the questionnaire, 192 progression events were documented, including 168 (88%) biochemical recurrences, 7 (4%) bone metastases, and 17 (9%) deaths related to prostate cancer as the first recorded event (a total of 73 men had documented PCSM, most with another progression event prior to PCSM). Secondary treatment did not account for any of the progression events.

Participants with higher inflammatory diet indices (EDIP) had an increased risk of prostate cancer progression ($HR_{per\ 1\text{-}SD}$= 1.27, 95% CI: 1.17-1.37), amounting to a 2.61-fold (95% CI: 1.75-3.90; p_{trend} <0.01) higher risk in those in the highest versus the lowest quintile of EDIP [Table 3]. Those with more insulinemic diets (EDIH) also had a higher risk of progression ($HR_{per\ 1\text{-}SD}$ =1.24, 95% CI: 1.05-1.46), amounting to a 1.63-fold (95% CI: 0.93-2.86; p_{trend}=0.05) higher risk among those in the highest versus lowest quintile. The hyperinsulinemic lifestyle index (ELIH) was similarly associated with progression ($HR_{per\ 1\text{-}SD}$ =1.34, 95% CI: 1.17-1.54), with a 2.81-fold (95% CI: 1.78-4.43; p_{trend}<0.01) higher risk of progression among those in the highest versus lowest quintile of the index. There was suggestive evidence that the insulin resistance dietary index (EDIR) was associated with prostate cancer progression ($HR_{per\ 1\text{-}SD}$=1.22, 95% CI: 1.00-1.48), though results from the models with EDIR modeled as quintiles were not statistically significant ($HR_{Q5\ vs\ Q1}$=1.38, 95% CI: 0.62-3.11; p_{trend}=0.45). The insulin resistance lifestyle index (ELIR) was statistically significantly associated with a higher risk of prostate cancer progression ($HR_{per\ 1\text{-}SD}$ =1.36, 95% CI: 1.12-1.64), reflecting a 2.43-fold (95% CI: 1.45-4.07; p_{trend}<0.01) higher risk of progression for those with the highest versus lowest quintile of the index [Table 3].

There was no convincing evidence of associations with PCSM (Table 3), though power for these analyses was limited. There was also no evidence of interaction between any of the dietary indices and BMI.

Results from the Cox proportional hazards models for progression were very similar to those from the Parametric (Weibull) survival models, and there was no evidence that competing events impacted the results (Supplemental Table S3). Multiple imputation resulted in 2,053 complete cases across all covariates and retainment of all 192 events in the multivariable models (Supplemental Table S4). The results were qualitatively unchanged from the primary analysis. The supplemental material also includes results from the simple (i.e., not fully adjusted) models [Supplemental Table S5].

DISCUSSION

In these analyses, we evaluated associations of three dietary (EDIP, EDIH, EDIR) and two lifestyle (ELIH, ELIR) indices – previously developed to estimate concentrations of biomarkers for the underlying inflammatory and insulin pathways – with prostate cancer progression and PCSM. Findings from this study suggest that diets with high inflammatory or insulinemic potential following a prostate cancer diagnosis are associated with a 2.61-fold and 1.63-fold higher risk of prostate cancer progression, respectively, for those in the highest versus lowest quintiles. The evidence was weaker, but still consistent with a positive association, for diets promoting insulin resistance.

The hyperinsulinemic and insulin resistance *lifestyle* indices also demonstrated strong associations with prostate cancer progression. Individuals in the highest versus lowest quintile of the ELIH and ELIR had a 2.8-fold and 2.4-fold higher risk of progression, respectively. These results are consistent with prior work demonstrating that the correlation between the lifestyle indices and circulating biomarkers was more than twice the correlation

observed with the diet-only indices.[14] These findings are also consistent with the World Cancer Research Fund/American Institute for Cancer Research report, which found adiposity to be the single most consistent factor predisposing men to higher risk of fatal prostate cancer.[38] Therefore, lifestyle changes that include more physical activity and achieving a healthy weight, in addition to low insulinemic and inflammatory diets, may lower risk of progression.

Although, to our knowledge, no study has examined these dietary and lifestyle indices in men with prostate cancer, these findings are consistent with our current understanding of the role of the inflammation and insulin pathways in promoting cancer growth and development. This report adds to our understanding of how these pathways may promote prostate cancer progression. Specifically, insulin is a potent growth factor that promotes cell metabolism and mitogenic processes, and cancer cells have been shown to have a disproportionally higher expression of insulin receptors than normal cells.[39,40] The EDIH has also been associated with a higher risk of prostate cancer development among previously disease-free men.[20,41] Thus, it is plausible that higher levels of circulating insulin would promote prostate cancer progression.[5] Inflammation can also act to promote insulin production,[5] and has been independently linked to prostate cancer risk.[42] For example, IL-6, a prominent inflammatory biomarker, has been shown to promote proliferation of prostate cells and inhibit cell death, and may be involved in the transition to metastatic disease.[7] The EDIP has also been associated with increased risk of incident lethal prostate cancer among men under 65 years of age.[20] Thus, it is also plausible that diets promoting inflammatory processes would promote cancer progression.

We observed a correlation between all three dietary indices, which is not surprising given the inflammatory and insulin pathways are interrelated.[5,43] Indeed, prior research found that the EDIP was associated with biomarkers of hyperinsulinemia and that the EDIH was associated with biomarkers of inflammation.[41,44] Similarly, although the insulin resistance and hyperinsulinemic indices were developed to predict different biomarkers,[14] hyperinsulinemia is a consequence of prolonged insulin resistance.[5] Recent work found that the EDIH is predictive of both insulin secretion *and* insulin resistance,[45] which may explain why the EDIR was not as strongly associated with prostate cancer progression as the EDIH in these analyses.

We did not find statistically significant evidence of associations between any of the indices and PCSM. While other mechanisms for the lack of associations cannot be ruled out, our results may reflect the relatively small number of cause-specific deaths in this cohort of men diagnosed with non-metastatic prostate cancer. Further research is needed to understand whether the relevant biological mechanisms are associated with PCSM among men with prostate cancer.

The inflammatory, hyperinsulinemic, and insulin resistance dietary indices were developed to predict inflammatory and insulinemic biomarkers associated with whole diet, and were not developed specific to any type of cancer. Recently, these indices have been associated with colorectal cancer incidence and mortality, [16,46] highlighting the role of inflammatory and insulin pathways across cancers.[5] Readers should focus on the importance of tailoring

whole diets following a prostate cancer diagnosis to collectively minimize consumption of inflammatory foods and those known to over-stimulate insulin secretion, and avoid focusing on the role of any given component of these indices.

There are several limitations of our study. Measurement error is a known limitation of self-reported diet data. However, the FFQ used in this proposal has been reported to be valid and reproducible and to perform well compared to 1-week diet records and in repeated FFQs one-year apart.[23] Men who self-select to participate in diet and lifestyle studies may also be relatively healthy compared to prostate cancer survivors who opt out. Men in our study predominately identified as white race, and 77% reported having at least some college-level education. While the generalizability of our results may thus be limited, the dietary indices have been applied in multiethnic samples and found to predict risk of developing type 2 diabetes with heightened risk among African- American and Hispanic women compared to European-American women.[47] Additionally, although multiple imputation was utilized to address missingness in covariates, these methods rely on the assumption that data are missing at random, which cannot readily be assessed.

In conclusion, in this cohort of men diagnosed with non-metastatic prostate cancer, diets with higher inflammatory and insulinemic potential were associated with higher risk of prostate cancer progression. Insulinemic lifestyle indices that included diet, physical activity, and BMI, were also associated with risk of disease progression. These findings add to the evidence that inflammation and insulin pathways influence prostate cancer progression and suggest that modifiable health habits may improve prostate cancer clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant and clinical characteristics of 2,056 men diagnosed with non-metastatic prostate cancer by quintile of inflammatory, hyperinsulinemia, and insulin resistance dietary indices

	Empirical Dietary Inflammatory Pattern (EDIP)					Empirical Dietary Index for Hyperinsulinemia (EDIH)					Empirical Dietary index for insulin Resistance (EDIR)				
Quintile:	**1st**	**2nd**	**3rd**	**4th**	**5th**	**1st**	**2nd**	**3rd**	**4th**	**5th**	**1st**	**2nd**	**3rd**	**4th**	**5th**
Point Range:	**−2.6 to −0.3**	**>−0.3 to −0.1**	**>−0.1 to 0.0**	**>0.0 to 0.2**	**>0.2 to 2.3**	**−1.1 to 0.1**	**>0.1 to 0.3**	**>0.3 to 0.4**	**>0.4 to 0.6**	**>0.6 to 2.2**	**−1.7 to −0.2**	**>−0.2 to 0.1**	**>0.1 to 0.3**	**>0.3 to 0.5**	**>0.5 to 2.6**
N	412	411	411	411	411	412	411	411	411	411	412	411	411	411	411
Age (years), mean (SD)	63.5 (7.9)	64.5 (8.0)	64.7 (8.0)	64.8 (8.0)	64.7 (7.9)	64.5 (7.7)	64.9 (7.8)	64.7 (8.2)	64.1 (7.8)	64.0 (8.3)	63.6 (7.6)	64.5 (7.5)	64.8 (8.4)	64.6 (7.8)	64.6 (8.4)
White, n (%)	394 (96)	390 (95)	396 (96)	396 (96)	377 (92)	392 (95)	389 (95)	392 (95)	394 (96)	386 (94)	398 (97)	394 (96)	385 (94)	396 (96)	380 (92)
BMI (kg/m^2), mean (SD)	27.1 (3.7)	27.3 (4.0)	27.3 (4.1)	27.6 (4.5)	28.3 (4.9)	26.3 (3.4)	27.2 (4.2)	27.4 (4.0)	28.3 (4.4)	28.5 (4.9)	26.9 (3.5)	27.3 (4.3)	27.2 (4.1)	27.7 (4.3)	28.5 (4.9)
<18.5, n (%)	0 (0)	1 (<1)	2 (<1)	4 (1)	3 (1)	1 (<1)	3 (1)	1 (<1)	2 (<1)	3 (1)	1 (<1)	0 (0)	4 (1)	2 (<1)	3 (1)
18.5 to <25, n (%)	121 (29)	113 (27)	123 (30)	104 (25)	93 (23)	141 (34)	131 (32)	114 (28)	82 (20)	86 (21)	126 (31)	127 (31)	112 (27)	107 (26)	82 (20)
25 to <30, n (%)	225 (55)	220 (54)	203 (49)	205 (50)	186 (45)	222 (54)	200 (49)	207 (50)	213 (52)	197 (48)	220 (53)	205 (50)	212 (52)	201 (49)	201 (49)
≥30, n (%)	66 (16)	77 (19)	83 (20)	98 (24)	129 (31)	48 (12)	77 (19)	89 (22)	114 (28)	125 (30)	65 (16)	79 (19)	83 (20)	101 (25)	125 (30)
Physical Activity (MET-hours/ week), mean (SD)	24.3 (26.2)	23.0 (31.5)	21.3 (29.5)	17.9 (23.8)	18.8 (25.3)	26.2 (33.8)	21.4 (26.5)	19.4 (22.2)	18.4 (25.6)	19.9 (27.4)	22.9 (28.4)	24.3 (31.0)	21.0 (27.9)	18.6 (23.2)	18.6 (26.1)
Smoking Status, n (%)															
Never	158 (39)	182 (45)	191 (47)	196 (48)	187 (47)	186 (45)	174 (43)	197 (48)	184 (45)	173 (43)	142 (35)	195 (48)	195 (48)	190 (47)	192 (48)
Former	232 (57)	205 (50)	188 (46)	196 (48)	189 (47)	206 (50)	212 (53)	196 (48)	200 (49)	196 (49)	250 (61)	188 (46)	192 (48)	193 (47)	187 (46)
Current	17 (4)	19 (5)	26 (6)	18 (4)	25 (6)	17 (4)	17 (4)	16 (4)	22 (5)	33 (8)	17 (4)	22 (5)	17 (4)	25 (6)	24 (6)
Family History of PC, n (%)	81 (20)	77 (19)	94 (23)	87 (21)	73 (18)	85 (21)	77 (19)	85 (21)	77 (19)	88 (21)	75 (18)	78 (19)	89 (22)	80 (19)	90 (22)
Clinical T-Stage, n (%)															
≤T1	235 (57)	237 (58)	232 (56)	236 (57)	242 (59)	247 (60)	239 (58)	227 (55)	239 (58)	230 (56)	247 (60)	232 (56)	242 (59)	225 (55)	236 (57)
T2	175 (42)	169 (41)	174 (42)	173 (42)	164 (40)	164 (40)	170 (41)	177 (43)	169 (41)	175 (43)	162 (39)	173 (42)	168 (41)	183 (45)	169 (41)
T3a	2 (<1)	5 (1)	5 (1)	2 (<1)	5 (1)	1 (<1)	2 (<1)	7 (2)	3 (1)	6 (1)	3 (1)	6 (1)	1 (<1)	3 (1)	6 (1)
Diagnostic Gleason, n (%)															

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2023 March 02.

	Empirical Dietary Inflammatory Pattern (EDIP)					Empirical Dietary Index for Hyperinsulinemia (EDIH)					Empirical Dietary index for insulin Resistance (EDIR)				
Quintile:	**1st**	**2nd**	**3rd**	**4th**	**5th**	**1st**	**2nd**	**3rd**	**4th**	**5th**	**1st**	**2nd**	**3rd**	**4th**	**5th**
Point Range:	**−2.6 to −0.3**	**>−0.3 to −0.1**	**>−0.1 to 0.0**	**>0.0 to 0.2**	**>0.2 to 2.3**	**−1.1 to 0.1**	**>0.1 to 0.3**	**>0.3 to 0.4**	**>0.4 to 0.6**	**>0.6 to 2.2**	**−1.7 to −0.2**	**>−0.2 to 0.1**	**>0.1 to 0.3**	**>0.3 to 0.5**	**>0.5 to 2.6**
<7	276 (68)	291 (71)	271 (67)	274 (67)	260 (64)	275 (67)	298 (74)	264 (65)	283 (69)	252 (62)	281 (69)	274 (67)	279 (69)	272 (67)	266 (65)
7	106 (26)	98 (24)	106 (26)	106 (26)	122 (30)	117 (29)	84 (21)	115 (28)	101 (25)	121 (30)	110 (27)	115 (28)	97 (24)	108 (26)	108 (26)
>7	25 (6)	18 (4)	30 (7)	29 (7)	27 (7)	18 (4)	23 (6)	29 (7)	25 (6)	34 (8)	18 (4)	18 (4)	30 (7)	29 (7)	34 (8)
Diagnostic PSA (ng/mL), median (IQR)	5.3 (4.3, 7.0)	5.4 (4.3, 8.1)	5.5 (4.4, 7.7)	5.7 (4.4, 8.2)	5.8 (4.5, 7.9)	5.4 (4.3, 7.3)	5.5 (4.4, 7.7)	5.6 (4.3, 7.7)	5.5 (4.2, 7.6)	5.8 (4.5, 8.7)	5.3 (4.3, 7.0)	5.5 (4.3, 8.2)	5.7 (4.5, 7.9)	5.7 (4.3, 8.4)	5.6 (4.4, 7.9)
Primary Treatment, n (%)															
Radical Prostatectomy	272 (67)	254 (63)	248 (62)	237 (59)	235 (59)	262 (65)	247 (62)	246 (62)	255 (63)	236 (59)	269 (66)	255 (64)	226 (58)	256 (64)	240 (60)
AS/WW	23 (6)	27 (7)	29 (7)	29 (7)	16 (4)	27 (7)	33 (8)	25 (6)	20 (5)	19 (5)	26 (6)	22 (5)	39 (10)	15 (4)	22 (6)
RT/ Brachytherapy	83 (21)	83 (21)	88 (22)	89 (22)	104 (26)	84 (21)	91 (23)	83 (21)	95 (24)	94 (23)	91 (22)	85 (21)	90 (23)	98 (24)	83 (21)
Hormone Therapy	19 (5)	16 (4)	21 (5)	23 (6)	24 (6)	14 (3)	17 (4)	27 (7)	21 (5)	24 (6)	13 (3)	16 (4)	23 (6)	18 (4)	33 (8)
Other	6 (1)	21 (5)	12 (3)	23 (6)	20 (5)	15 (4)	12 (3)	16 (4)	11 (3)	28 (7)	7 (2)	23 (6)	15 (4)	15 (4)	22 (6)

Abbreviations: AS/WW – Active Surveillance/Watchful Waiting; BMI – body mass index; IQR – interquartile range; MET – metabolic equivalent of task; PC – prostate cancer; PSA – prostate-specific antigen (ng/mL); RT – radiotherapy; SD – standard deviation

Table 2.

Participant and clinical characteristics of 2,056 men diagnosed with non-metastatic prostate cancer by quintile of hyperinsulinemia and insulin resistance lifestyle indices

	Empirical Lifestyle Index for Hyperinsulinemia (ELIH)					Empirical Lifestyle Index for Insulin Resistance (ELIR)				
Quintile:	**1st**	**2nd**	**3rd**	**4th**	**5th**	**1st**	**2nd**	**3rd**	**4th**	**5th**
Point Range:	**0.2 to 1.1**	**>1.1 to 1.2**	**>1.2 to 1.4**	**>1.4 to 1.5**	**>1.5 to 2.7**	**0.2 to 1.2**	**>1.2 to 1.4**	**>1.4 to 1.5**	**>1.5 to 1.7**	**>1.7 to 3.4**
N	412	411	411	411	411	412	411	411	411	411
Age (years), mean (SD)	65.3 (8.4)	65.3 (8.1)	63.9 (7.9)	64.1 (7.9)	63.6 (7.4)	64.7 (7.9)	64.2 (8.3)	65.1 (7.6)	64.5 (8.1)	63.7 (7.7)
White, n (%)	389 (94)	395 (96)	387 (94)	389 (95)	393 (96)	396 (96)	390 (95)	393 (96)	391 (95)	383 (93)
BMI (kg/m^2), mean (SD)	23.6 (2.3)	25.3 (2.0)	27.0 (2.1)	28.6 (2.3)	33.1 (4.4)	24.6 (2.8)	25.8 (2.7)	27.1 (3.0)	28.2 (3.1)	31.9 (5.1)
<18.5, n (%)	10 (2)	0 (0)	0 (0)	0 (0)	0 (0)	7 (2)	1 (<1)	2 (<1)	0 (0)	0 (0)
18.5 to <25, n (%)	285 (69)	180 (44)	62 (15)	21 (5)	6 (1)	224 (54)	157 (38)	92 (22)	57 (14)	24 (6)
25 to <30, n (%)	117 (28)	225 (55)	316 (77)	287 (70)	94 (23)	170 (41)	228 (55)	254 (62)	248 (60)	139 (34)
≥30, n (%)	0 (0)	6 (1)	33 (8)	103 (25)	311 (76)	11 (3)	25 (6)	63 (15)	106 (26)	248 (60)
Physical Activity (MET-hours/week), mean (SD)	33.1 (40.4)	20.9 (22.2)	20.8 (26.0)	16.1 (19.5)	14.4 (19.6)	30.8 (37.5)	22.0 (26.1)	19.3 (23.1)	17.3 (24.3)	15.9 (20.7)
Smoking Status, n (%)										
Never	192 (47)	180 (44)	192 (48)	163 (40)	187 (46)	171 (42)	192 (47)	180 (44)	183 (46)	188 (46)
Former	192 (47)	197 (49)	194 (49)	223 (54)	204 (50)	215 (53)	190 (47)	216 (53)	190 (47)	199 (49)
Current	24 (6)	29 (7)	13 (3)	24 (6)	15 (4)	21 (5)	24 (6)	13 (3)	28 (7)	19 (5)
Family History of PC, n (%)	89 (22)	73 (18)	81 (20)	80 (19)	89 (22)	75 (18)	89 (22)	74 (18)	80 (19)	94 (23)
Clinical T-Stage, n (%)										
≤T1	248 (60)	227 (55)	246 (60)	238 (58)	223 (54)	246 (60)	224 (55)	240 (58)	231 (56)	241 (59)
T2	158 (38)	180 (44)	163 (40)	170 (41)	184 (45)	161 (39)	185 (45)	166 (40)	178 (43)	165 (40)
T3a	6 (1)	4 (1)	2 (<1)	3 (1)	4 (1)	5 (1)	2 (<1)	5 (1)	2 (<1)	5 (1)
Diagnostic Gleason, n (%)										
<7	296 (73)	267 (65)	287 (70)	271 (66)	251 (62)	283 (69)	283 (70)	281 (68)	267 (65)	258 (64)
7	93 (23)	116 (28)	93 (23)	114 (28)	122 (30)	109 (27)	101 (25)	103 (25)	118 (29)	107 (26)
>7	18 (4)	25 (6)	28 (7)	23 (6)	35 (9)	16 (4)	21 (5)	27 (7)	24 (6)	41 (10)
Diagnostic PSA (ng/mL), median (IQR)	5.5 (4.3, 7.4)	5.8 (4.5, 7.7)	5.4 (4.3, 7.6)	5.5 (4.2, 7.9)	5.7 (4.4, 8.2)	5.6 (4.4, 7.4)	5.4 (4.2, 7.7)	5.6 (4.5, 7.8)	5.7 (4.3, 8.1)	5.6 (4.4, 8.1)
Primary Treatment, n (%)										

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2023 March 02.

	Empirical Lifestyle Index for Hyperinsulinemia (ELIH)					Empirical Lifestyle Index for Insulin Resistance (ELIR)				
Quintile:	**1st**	**2nd**	**3rd**	**4th**	**5th**	**1st**	**2nd**	**3rd**	**4th**	**5th**
Point Range:	**0.2 to 1.1**	**>1.1 to 1.2**	**>1.2 to 1.4**	**>1.4 to 1.5**	**>1.5 to 2.7**	**0.2 to 1.2**	**>1.2 to 1.4**	**>1.4 to 1.5**	**>1.5 to 1.7**	**>1.7 to 3.4**
Radical Prostatectomy	251 (63)	247 (62)	258 (64)	252 (62)	238 (60)	270 (67)	245 (62)	239 (60)	253 (63)	239 (60)
AS/WW	26 (7)	23 (6)	24 (6)	24 (6)	27 (7)	25 (6)	26 (7)	30 (8)	24 (6)	19 (5)
RT/Brachytherapy	87 (22)	94 (23)	88 (22)	90 (22)	88 (22)	83 (20)	89 (22)	98 (24)	83 (21)	94 (24)
Hormone Therapy	20 (5)	20 (5)	16 (4)	22 (5)	25 (6)	13 (3)	20 (5)	19 (5)	22 (6)	29 (7)
Other	14 (4)	17 (4)	15 (4)	16 (4)	20 (5)	14 (3)	17 (4)	14 (4)	18 (4)	19 (5)

Abbreviations: AS/WW – Active Surveillance/Watchful Waiting; BMI – body mass index (kg/m^2); IQR – interquartile range; MET – metabolic equivalent of task; PC – prostate cancer; PSA – prostate-specific antigen (ng/mL); RT – radiotherapy; SD – standard deviation

Table 3.

Multivariable models estimating associations of post-diagnostic inflammatory, hyperinsulinemia, and insulin resistance diets and lifestyles with the risk of prostate cancer progression and prostate cancer-specific mortality among men diagnosed with non-metastatic prostate cancer

	Prostate Cancer Progression[a,b]				
	EDIP	**EDIH**	**EDIR**	**ELIH**	**ELIR**
Events	175	175	175	175	175
N	1,875	1,875	1,875	1,875	1,875
Continuous					
Per 1-SD unit	1.27 (1.17, 1.37)	1.24 (1.05, 1.46)	1.22 (1.00, 1.48)	1.34 (1.17, 1.54)	1.36 (1.12, 1.64)
Quintile					
1st	Ref	Ref	Ref	Ref	
2nd	2.21 (1.25, 3.89)	1.27 (0.83, 1.95)	1.28 (0.63, 2.60)	1.66 (1.08, 2.54)	1.62 (1.03, 2.56)
3rd	2.60 (1.54, 4.39)	1.29 (0.79, 2.12)	1.51 (0.74, 3.10)	1.69 (0.86, 3.35)	1.27 (0.74, 2.19)
4th	1.91 (1.14, 3.20)	1.61 (1.03, 2.51)	1.32 (0.61, 2.85)	2.82 (1.93, 4.11)	1.95 (1.12, 3.37)
5th	2.61 (1.75, 3.90)	1.63 (0.93, 2.86)	1.38 (0.62, 3.11)	2.81 (1.78, 4.43)	2.43 (1.45, 4.07)
p-trend	**<0.01**	**0.05**	**0.45**	**<0.01**	**<0.01**
	Prostate Cancer-Specific Mortality[a,c]				
	EDIP	**EDIH**	**EDIR**	**ELIH**	**ELIR**
Events	60	60	60	60	60
N	2,198	2,198	2,198	2,198	2,198
Continuous					
Per 1-SD unit	1.15 (0.92, 1.44)	1.22 (0.97, 1.55)	1.14 (0.84, 1.55)	1.22 (0.90, 1.66)	1.16 (0.83, 1.62)
Quintile					

	Prostate Cancer Progression[a,b]				
	EDIP	**EDIH**	**EDIR**	**ELIH**	**ELIR**
1st	Ref	Ref	Ref	Ref	Ref
2nd	1.00 (0.34, 2.91)	1.66 (0.76, 3.62)	2.28 (0.76, 6.87)	1.85 (0.78, 4.43)	1.04 (0.43, 2.47)
3rd	1.03 (0.39, 2.74)	1.09 (0.35, 3.40)	1.92 (0.55, 6.71)	0.87 (0.29, 2.54)	0.75 (0.25, 2.23)
4th	1.77 (0.68, 4.58)	1.69 (0.65, 4.42)	2.02 (0.58, 7.06)	1.95 (0.82, 4.63)	0.74 (0.24, 2.26)
5th	1.31 (0.47, 3.67)	1.58 (0.65, 3.86)	2.50 (0.83, 7.53)	2.20 (0.76, 6.34)	1.37 (0.44, 4.29)
p-trend	**0.30**	**0.39**	**0.24**	**0.17**	**0.83**

Abbreviations: BMI – body mass index; CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor; EDIH – empirical dietary index for hyperinsulinemia; EDIP – empirical dietary inflammatory pattern; EDIR – empirical dietary index for insulin resistance; ELIH – empirical lifestyle index for hyperinsulinemia; ELIR – empirical lifestyle index for insulin resistance; MET – metabolic equivalent of task; PCSM – prostate cancer specific mortality; PSA – prostate specific antigen; SD – standard deviation

[a]Models were adjusted for age at diagnosis (continuous), time between diagnosis and questionnaire completion date (continuous), and CaPSURE clinical site, race (white, other), T stage at diagnosis (≤T1, T2, T3a), Gleason at diagnosis (<7, 7, >7), PSA at diagnosis (≤6, >6 to 10, >10), primary treatment (radical prostatectomy, radiation, hormonal therapy, watchful waiting/active surveillance, other), family history of prostate cancer in bother or father (yes/no), BMI (continuous), physical activity (total MET-hours/week; continuous), smoking (never, former, current), alcohol (continuous), supplement use (yes/no), and total energy intake

[b]Estimated via parametric (Weibull) survival models to account for interval censoring. A total of 2,056 met inclusion for progression analyses.

[c]Estimated via Cox proportional hazards models. A total of 2,447 men met inclusion for PCSM analyses, as men who were excluded from progression analysis due to having a documented progression event prior to questionnaire were included in this analysis