Inflammatory and Insulinemic Dietary Patterns: Influence on Circulating Biomarkers and Prostate Cancer Risk

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ABSTRACT

Prostate cancer is common in countries with affluent dietary patterns and represents a heterogeneous collection of subtypes with varying behavior. Reductionist strategies focusing on individual nutrients or foods have not clearly defined risk factors. We have developed mechanisms-based dietary patterns focusing upon inflammation and chronic insulin hypersecretion, processes that are hypothesized to impact prostate carcinogenesis. In the Prostate, Lung, Colorectal, and Ovarian cancer cohort, we calculated the empirical dietary index for hyperinsulinemia (EDIH) and empirical dietary inflammatory pattern (EDIP) scores from food frequency questionnaire data among 3,517 men and women who provided a blood sample at enrollment. We used these scores in multivariable-adjusted linear regression to validate EDIH and EDIP against relevant circulating biomarkers. In a separate sample of 49,317 men, we used multivariable-adjusted Cox regression to evaluate associations of EDIH and EDIP with prostate cancer (total and subtypes) risk. Participants consuming the most hyperinsulinemic diets (EDIH quintile 5) had significantly higher concentrations of C-peptide, insulin, c-reactive protein, TNFα-R2, and lower adiponectin, than those in quintile 1. Similarly, participants consuming the most proinflammatory diets had significantly higher concentrations of IL6, TNFα-R2, C-peptide, insulin, and lower adiponectin. Men consuming hyperinsulinemic diets were at higher total prostate cancer risk: HRquintile5vs1, 1.11; 95% confidence interval (CI), 1.01–1.23; P trend = 0.03, especially high-grade cancer: HRquintile5vs1, 1.18; 95% CI, 1.02–1.37; P trend = 0.06. The EDIP was not associated with prostate cancer risk. In summary, EDIH and EDIP predicted concentrations of known insulinemic and inflammatory biomarkers, and EDIH further predicted risk of future prostate cancer. Interventions to reduce the adverse role of hyperinsulinemic diets may be a means of prostate cancer prevention.

Introduction

Prostate cancer is common in countries with affluent dietary patterns and represents a heterogeneous collection of subtypes with varying behavior. It is the most common cancer among men in the United States (1). According to the NCI, the lifetime risk of developing prostate cancer among U.S. men is 11.6% (2). Cancers have a multifactorial etiology, and diet is a modifiable factor linked to the risk of developing several cancers, including prostate cancer (3). Most studies of the association of diet and prostate cancer risk have focused on individual dietary components, with some studies showing suggestive evidence linking specific dietary factors with prostate cancer risk. For example, higher intake of lycopene linked with lower prostate cancer risk and higher intake of dairy associated with higher prostate cancer risk (4–6). However, most studies have shown mixed findings on individual dietary factors and prostate cancer risk, which may not be surprising given that studies of single nutrients and foods do not account for complex interactions inherent in whole diets.

The examination of whole diets or dietary patterns in relation to disease risk is an appealing approach that has been adopted in nutritional epidemiology. Hyperinsulinemia and inflammation are two interrelated biological pathways that have been linked with prostate cancer risk (7–9). Therefore, dietary patterns that directly influence these biological pathways may be more predictive of prostate cancer risk than dietary patterns not related to these pathways. Our team developed two empirical hypothesis-oriented dietary patterns: the empirical dietary index for hyperinsulinemia (EDIH) score to assess the potential of the diet to contribute to hyperinsulinemia (10) and the empirical dietary inflammatory pattern (EDIP) score to assess the inflammatory potential of the

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diet (11). In the current study, our objectives were 2-fold: (i) to validate the two dietary indices in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer cohort by determining their associations with concentrations of relevant circulating biomarkers, and (ii) to investigate the associations between the dietary indices and risk of developing prostate cancer, including prostate cancer subtypes.

Materials and Methods

Study population

The PLCO cancer screening trial was a large randomized clinical trial sponsored by the NCI, which involved ten sites around the United States (refs. 12, 13; ClinicalTrials.gov identifier: NCT00002540). The trial enrolled 154,901 participants (77,445 in the intervention arm and 76,456 in the control arm) aged 55 to 74 years between 1993 and 2001 and studied the effect of cancer screening on mortality (13). Baseline characteristics and dietary information were obtained from all participants at trial initiation (12). The PLCO study was approved by Institutional Review Boards at the NCI and the National Human Genome Research Institute in the United States. All participants provided written informed consent.

For participants in the intervention arm, blood was collected yearly from randomization (year 0) to year 5 except year 3. Circulating biomarkers have been assessed in several nested case–control studies using these blood samples (14–27). Of the 77,445 participants in the intervention arm, 3,951 had at least one biomarker of interest and dietary information. After excluding participants with incomplete dietary information, high c-reactive protein (CRP >10 mg/L), which could be reflective of ongoing infection, very low body mass index (BMI; <15 kg/m^2), and very high BMI (>50 kg/m^2), 3,517 men and women were retained for analyses of our first objective: to assess the associations of the two dietary indices with circulating biomarker concentrations in cross-sectional analyses (Supplementary Fig. S1).

Prospective analyses of the associations of the dietary indices with risk of developing prostate cancer included a separate sample of 76,678 men from both arms of the trial. After excluding men who had prostate cancer diagnosed prior to completing the diet history questionnaire (DHQ), those without dietary data or who had extreme values for total energy intake (below 1 percentile or above 99th percentile), and those whose prostate cancer was a secondary primary, we retained 49,317 men in the final analyses (Supplementary Fig. S1).

Diet assessment and calculation of dietary index scores

Diet was assessed using two validated semiquantitative food frequency questionnaires: the dietary questionnaire (DQX) that included 137 food items, and DHQ that included 124 food items. Both questionnaires ascertained the usual dietary intake of participants in the previous 12 months (12). The food items listed in the DQX and DHQ were commonly consumed in the general population in the United States at the time of diet assessment. The DQX was designed based on two previously validated food frequency questionnaires (28, 29). The DHQ was validated against four 24-hour dietary recalls covering the same 12-month period as the DHQ in the Eating Table study (30). The DQX was completed at baseline for participants in the intervention arm within 1 year of blood donation; therefore, we used dietary data from the DQX for the biomarker analysis. The DHQ was introduced 5 years into the trial and completed by 77% of participants in both study arms (12). Therefore, we used dietary data from the DHQ for the prostate cancer analysis.

Details on the development and validation of the EDIH and EDIP indices have previously been described (10, 31). We calculated scores for the two dietary indices using dietary data from the DQX and DHQ. Briefly, the EDIH score was developed in a sample of 5,812 women in the Nurses' Health Study (NHS), to empirically create a score to measure the insulinemic potential of whole diets defined using food groups (10). Thirty-nine predefined food groups in servings/day were entered into stepwise linear regression analyses to identify a dietary pattern most predictive of plasma c-peptide concentrations as surrogate marker for insulin secretion (32). The EDIP score was developed in a separate study using a sample of 5,230 women in the NHS (11). The goal was to empirically create a score for overall inflammatory potential of whole diets defined using food groups. Thirty-nine food groups were entered into reduced rank regression models followed by stepwise linear regression analyses to identify a dietary pattern most predictive of three plasma markers of inflammation: CRP, IL6, and TNFα-R2.

Both the EDIH and EDIP scores are weighted sums of 18 food groups and assess the insulinemic or inflammatory potential of the diet, respectively, on a continuum from maximally low insulinemic or anti-inflammatory to maximally hyperinsulinemic or proinflammatory potential, respectively. That is, lower (more negative) scores indicate low insulinemic/low inflammatory diets, and higher (more positive) scores indicate high insulinemic/proinflammatory diets. Both scores were evaluated for validity in independent samples of men and women using dietary and biomarker data from NHS-II (a cohort of younger women different than NHS) and Health Professionals Follow-up Study, a cohort of male health professionals (10, 11). The component foods for both dietary indices in the PLCO cohort are listed in Supplementary Table S1.

Biomarker assessment

We pooled biomarker data from 14 studies nested within the intervention arm of PLCO. These studies assessed the following six biomarkers in fasting serum samples: CRP, adiponectin, IL6, TNFα-R2, c-peptide, and insulin. CRP was measured using one of the following assays: a chemiluminescent immunoassay (14, 20, 25), ELISA (21), Luminex bead–based assay (22, 24, 26), multiplex assays for use on a Luminex multianalyte profiling (xMAP) system (15), and high-sensitivity nephelometric/turbidimetric assay (19).

Adiponectin was assessed by ELISA (17) or radioimmunoassay (17, 27). IL6 and TNFα-R2 were assessed by Luminex bead–based commercial assay panels (22), electrochemiluminescence immunoassay plates (25), or multiplex assays for use on a Luminex multianalyte profiling (xMAP) system (15). C-peptide was assessed by ELISA (17, 19). Insulin was measured via a radioimmunoassay (18). Intrabatch coefficients of variation for these assays ranged from 2.7% to 11.9%.

Prostate cancer ascertainment

Prostate cancer screening was conducted using digital rectal exam (DRE) at baseline, years 1, 2, and 3, and by PSA measurement at baseline and years 1 through 5 in all ten PLCO study centers. Participants who screened positive (a PSA test result >4.0 ng/mL or suspicious DRE result) were referred to primary healthcare physicians for further diagnostic examinations. During the follow-up period, prostate cancer incidence and deaths from any cause were ascertained primarily through a mailed annual questionnaire to update cancer diagnoses that occurred in the preceding year. Participants who did not return the questionnaire were re-mailed or contacted by telephone. The incident prostate cancer cases reported on the annual questionnaire were verified with medical records by trained medical records abstractors. Detailed information on prostate cancer diagnoses, including clinical stage and Gleason grade, was recorded.

Clinical stage and Gleason grade were used to classify prostate cancer into advanced or nonadvanced status. A Gleason score of 2–6 was used to define low-grade prostate cancer and a score of 7–10 for high-grade cancer, advanced prostate cancer was defined using pathologic stage T3, T4, N1, or M1 at diagnosis, or lymph node metastases, whereas lethal prostate cancer was defined as cases that metastasized to distant organs at diagnosis or over follow-up, or that caused prostate cancer death. The follow-up process also included periodic linkage of the participants' files to the National Death Index and notification of vital status by next of kin. Follow-up ended on December 31, 2013, or when a participant died, was lost to follow-up or at the end of the 13th year from randomization, whichever came first.

Statistical analysis

Baseline characteristics of the study population are presented in quintiles of EDIH and EDIP. Quintile cut points were determined from the distribution of the entire study population. Continuous variables were presented as means and SD and categorical variables as frequencies and percentages.

For the biomarker analyses, biomarker concentrations were log-transformed to normalize their distributions prior to analyses. To assess the association of EDIH and EDIP scores with concentrations of biomarkers, we conducted multivariable-adjusted linear regression analyses to model the log of biomarker concentrations as the outcome, and estimated the difference in biomarker concentrations in higher dietary index quintiles compared with the lowest quintile as the reference. We then back-transformed the biomarker concentrations to obtain an estimate of the relative difference as well as the absolute concentrations of each biomarker in quintiles of the EDIH and EDIP scores. All multivariable models were adjusted for the following potential confounding variables: total energy intake, age at blood draw, pack-years of smoking, physical activity, sex, education, marital status, race, PLCO study center, aspirin use, ibuprofen use, nested study case–control status, family history of cancer, and additionally for BMI in separate models. For analyses of linear trend, we used the EDIH and EDIP continuous score as 1 SD increments for each participant, in multivariable-adjusted models, and interpreted the *P* value of the continuous variable as the *P* value for linear trend. We explored potential effect modification of the association between the EDIH and EDIP, and circulating biomarker was assessed in categories of BMI and smoking status, using dietary index quartiles due to smaller sample size. In separate models, we tested for interaction using the Wald *P* value of the interaction term between dietary index and BMI or smoking.

For analyses on the risk of future prostate cancer, we used multivariable-adjusted Cox proportional hazards (PH) regression models to calculate HRs and associated 95% confidence intervals (CI) for the risk of total prostate cancer and prostate cancer subtypes (high grade, low grade, advanced, and lethal) in EDIH and EDIP quintiles. The PH assumption was assessed for each covariate using Martingale-based residuals, and no covariate was in violation. The lowest EDIH and EDIP quintiles (representing the least insulinemic and most anti-inflammatory diets, respectively) were the reference for all models. All multivariable-adjusted models included the following potential confounding variables: age at enrollment, BMI, smoking status, physical activity, education, race, family history of cancer, use of PSA screening tests, PLCO study center, aspirin use, ibuprofen use, chronic disease comorbidity score, and occupation. Potential effect modification of the association between the EDIH and EDIP, and prostate cancer and prostate cancer subtypes was explored in categories defined by BMI, smoking status, and race. Tests of linear trend between dietary indices and total prostate cancer and prostate cancer subtypes incidence were computed by using the EDIH and EDIP continuous score as 1-SD increments in multivariable-adjusted models. Due to reduced sample size, quartiles were used for the subgroup analysis. We assessed interactions for each potential effect modifier using the Wald *P* values of the interaction terms. All analyses were implemented using SAS version 9.4, and statistical significance was assessed in two-sided tests with *P* values <0.05.

Results

Biomarker analysis

The distribution of socio-demographic and health characteristics of participants with biomarker data is summarized in

Table 1. Characteristics of study participants in quintiles of the dietary indices in the biomarker sample.

Characteristic	Total population	EDIH score quintiles					EDIP score quintiles				
		Quintile 1 (−1.52, <0.04)	Quintile 2 (0.04, <0.23)	Quintile 3 (0.23, <0.43)	Quintile 4 (0.43, <0.72)	Quintile 5 (0.72, 3.43)	Quintile 1 (−5.89, <−1.26)	Quintile 2 (−1.26, <−0.78)	Quintile 3 (−0.78, <−0.42)	Quintile 4 (−0.42, <−0.05)	Quintile 5 (−0.05, 3.98)
Sample size	3,517	703	704	703	704	703	704	703	704	703	704
Age at baseline, years	64.1 ± 5.3	64.1 ± 5.2	64.6 ± 5.4	64.4 ± 5.3	63.7 ± 5.1	63.5 ± 5.2	63.5 ± 5.3	64.1 ± 5.2	64.1 ± 5.4	64.4 ± 5.2	64.3 ± 5.4
BMI (kg/m^2), %	27.1 ± 4.6	25.7 ± 4.3	26.7 ± 4.2	27.5 ± 4.8	27.6 ± 4.9	28.0 ± 4.6	26.4 ± 4.2	26.6 ± 4.6	26.9 ± 4.4	27.7 ± 4.8	27.9 ± 5.0
Normal weight (18.5–<25)	35	45.1	39.2	32.3	31.3	27.3	39.3	39.4	36.7	31.4	28.5
Overweight (25–<30)	42.9	39.7	42.8	44.0	41.6	46.4	43.1	40.9	44.4	42.8	43.2
Obese (≥30)	22.1	15.2	18.0	23.8	27.1	26.3	17.6	19.7	18.9	25.9	28.3
Smoking status, %											
Never	30.7	27.2	34.8	35.4	31.8	24.3	18.8	26.6	34.1	37.2	36.8
Current	24.5	24.8	19.3	19.8	25.7	33	32	25.7	22.3	18.5	24
Former	44.8	48.1	45.9	44.8	42.5	42.7	49.2	47.7	43.5	44.3	39.1
Pack-years of smoking	34.2 ± 36.2	30.0 ± 32.7	28.4 ± 34.5	31.4 ± 34.6	36.6 ± 37.7	44.7 ± 38.8	42.1 ± 37.3	34.6 ± 35.3	31.2 ± 35.1	30.2 ± 35.3	33.0 ± 36.8
Vigorous activity, hours/week	2.6 ± 1.8	2.8 ± 1.8	2.8 ± 1.8	2.5 ± 1.8	2.4 ± 1.8	2.4 ± 1.9	2.6 ± 1.8	2.6 ± 1.8	2.6 ± 1.8	2.5 ± 1.8	2.4 ± 1.9
Number of supplements used	12 ± 11	14 ± 11	13 ± 11	12 ± 11	12 ± 11	10 ± 11	12 ± 11	13 ± 11	12 ± 11	12 ± 11	11 ± 11
Family history of cancer, %	58.6	58.3	62.4	60.2	58.2	53.9	56.3	61.7	58.9	60.1	56.1
Female, %	50.0	66.7	60.2	54.6	41.8	26.6	46.2	55.7	55.2	49.9	43.0
Educational level, %											
<11 years	8.4	4.3	6.3	7.4	9.5	14.8	6.0	7.0	6.5	10.8	12.0
12 years or completed high school	24.2	21.8	25.0	25.6	23.6	25.0	20.3	25.3	23.5	24.7	27.2
Post high school training other than college	14.4	11.1	14.8	15.8	14.8	15.5	12.7	14.4	16.6	14.1	14.2
Some college	21.6	21.5	20.3	21.8	22.2	22.2	23.2	18.6	22.1	22.9	21.2
College graduate	16.4	22.5	16.8	13.9	15.5	13.1	19.8	17.8	17.8	12.1	14.4
Postgraduate	15.0	18.9	16.9	15.5	14.5	9.4	18.1	17.1	13.5	15.5	11.1
Aspirin use, %	49.4	48.8	49.9	47.7	50.7	49.9	50.8	51.4	46.5	49.7	48.5
Ibuprofen use, %	27.8	30.3	28.4	27.0	25.7	27.6	28	30.1	29.5	27.1	24.3
White race, %	93.2	95.6	94.6	92.3	93.3	90.0	96.7	95.6	94.2	91.2	88.2

Note: Values are presented as mean ± SD for continuous variables and percentages for categorical variables. Dietary indices were adjusted for total energy intake.

Table 1. The mean age of the participants was 64.1 ± 5.3 years, and 93.2% of the participants were European Americans. Participants with the most hyperinsulinemic or proinflammatory diets (EDIH and EDIP quintiles 5) had higher BMI and lower physical activity compared with participants with the lowest insulinemic and anti-inflammatory diets (EDIH and EDIP quintiles 1). Also, the proportions of participants who were overweight or obese, or had less than 11 years of education increased across the dietary index quintiles and were highest among those consuming the most hyperinsulinemic or proinflammatory diets (**Table 1**).

The percentage difference in concentrations of all six circulating biomarkers across EDIH and EDIP quintiles is presented in **Table 2**. The multivariable-adjusted (including additional adjustment for BMI) percentage difference and 95% CI in the highest compared with the lowest EDIH quintile were as follows: CRP, +19% (−1%, +42%), P trend = 0.001; adiponectin, −20% (−36%, 0%), P trend = 0.009; IL6, −1% (−24%, +29%); P trend = 0.26; TNFα-R2, +2% (−1%, +12%), P trend = 0.002; c-peptide, +20% (+2%, +41%), P trend = 0.03; and insulin +28% (+4%, +59%), P trend = 0.01. For EDIP quintile 5 versus 1: CRP, +16 (−3%, 39%); P trend = 0.16; adiponectin, −17% (−34%, 4%), P trend = 0.04; IL6, +32% (+1%, +72%), P trend = 0.04; TNFα-R2, +8% (+1%, +14%), P trend = 0.0005; c-peptide +14% (−3%, +34%), P trend = 0.02; and insulin +31% (+6%, +62%), P trend = 0.005. The absolute concentrations of all six biomarkers increased (or decreased for adiponectin) across dietary index quintiles (**Table 3**).

Supplementary Table S2 presents the percentage difference in concentrations of circulating biomarkers in BMI categories. For EDIH, though the interaction between EDIH and BMI was significant only in CRP models, associations between EDIH

Table 2. Multivariable-adjusted percent difference (95% CI) in the relative concentrations of circulating biomarkers in quintiles of the dietary indices.

Statistical model	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* trend	Per 1 SD increase in dietary score
			EDIH score quintiles				
CRP (n = 2,954)	590	591	591	591	591		
Multivariable (MV)-adjusted	0 (reference)	7 (−10, 29)	28 (7, 54)	30 (8, 56)	27 (6, 53)	<0.0001	11 (6, 16)
MV+BMI adjusted	0 (reference)	7 (−10, 27)	20 (1, 43)	21 (1, 45)	19 (−1, 42)	0.001	8 (3, 13)
Adiponectin (n = 605)	121	121	121	121	121		
Multivariable (MV)-adjusted	0 (reference)	−17 (−34, 4)	−31 (−45, −14)	−24 (−40, −6)	−29 (−43, −10)	0.0005	−10 (−15, −6)
MV+BMI adjusted	0 (reference)	−14 (−31, 7)	−26 (−41, −8)	−18 (−34, 2)	−20 (−36, 0)	0.009	−7 (−12, −2)
IL6 (n = 2,023)	404	405	405	405	404		
Multivariable (MV)-adjusted	0 (reference)	4 (−20, 34)	23 (−6, 59)	22 (−6, 59)	−1 (−24, 29)	0.26	4 (−3, 11)
MV+BMI adjusted	0 (reference)	4 (−20, 34)	23 (−6, 59)	22 (−6, 59)	−1 (−24, 29)	0.26	4 (−3, 11)
TNFα-R2 (n = 3,516)	703	703	704	703	703		
Multivariable (MV)-adjusted	0 (reference)	3 (−2, 10)	8 (2, 14)	8 (2, 14)	7 (1, 14)	0.0003	3 (1, 4)
MV+BMI adjusted	0 (reference)	3 (−3, 9)	6 (0, 13)	6 (0, 13)	5 (−1, 12)	0.002	2 (1, 4)
C-peptide (n = 962)	192	193	192	193	192		
Multivariable (MV)-adjusted	0 (reference)	8 (−8, 27)	9 (−8, 28)	9 (−8, 29)	26 (6, 49)	0.004	6 (2, 11)
MV+BMI adjusted	0 (reference)	7 (−9, 25)	7 (−9, 25)	5 (−11, 23)	20 (2, 41)	0.03	5 (1, 9)
Insulin (n = 961)	192	192	193	192	192		
Multivariable (MV)-adjusted	0 (reference)	15 (−8, 43)	14 (−9, 42)	32 (1, 65)	38 (10, 74)	0.001	10 (4, 16)
MV+BMI adjusted	0 (reference)	13 (−8, 40)	11 (−10, 37)	26 (1, 55)	28 (4, 59)	0.01	7 (2, 13)
			EDIP score quintiles				
CRP (n = 2,954)	590	591	591	591	591		
Multivariable (MV)-adjusted	0 (reference)	13 (−6, 35)	13 (−5, 36)	20 (0, 44)	30 (8, 57)	0.006	7 (2, 12)
MV+BMI adjusted	0 (reference)	11 (−6, 33)	8 (−10, 28)	11 (−7, 32)	16 (−3, 39)	0.16	3 (−1, 8)
Adiponectin (n = 605)	121	121	121	121	121		
Multivariable (MV)-adjusted	0 (reference)	−14 (−30, 8)	−19 (−35, 2)	−17 (−34, 5)	−28 (−43, −8)	0.003	−9 (−14, −3)
MV+BMI adjusted	0 (reference)	−13 (−30, 9)	−11 (−29, 11)	−11 (−28, 12)	−17 (−34, 4)	0.04	−6 (−11, 0)
IL6 (n = 2,023)	404	405	405	405	404		
Multivariable (MV)-adjusted	0 (reference)	22 (−6, 59)	9 (−16, 41)	36 (5, 77)	31 (1, 71)	0.04	7 (0, 15)
MV+BMI adjusted	0 (reference)	22 (−6, 59)	9 (−16, 41)	37 (5, 78)	32 (1, 72)	0.04	7 (0, 15)
TNFα-R2 (n = 3,516)	703	703	704	703	703		
Multivariable (MV)-adjusted	0 (reference)	4 (−2, 10)	6 (0, 13)	7 (1, 13)	10 (4, 17)	<0.0001	3 (2, 5)
MV+BMI adjusted	0 (reference)	4 (−2, 10)	5 (−1, 12)	6 (0, 12)	8 (1, 14)	0.0005	3 (1, 4)
C-peptide (n = 962)	192	193	192	193	192		
Multivariable (MV)-adjusted	0 (reference)	12 (−5, 33)	11 (−6, 31)	21 (2, 43)	21 (2, 43)	0.002	7 (2, 11)
MV+BMI adjusted	0 (reference)	15 (−2, 35)	12 (−4, 31)	19 (2, 40)	14 (−3, 34)	0.02	5 (1, 9)
Insulin (n = 961)	192	192	193	192	192		
Multivariable (MV)-adjusted	0 (reference)	7 (−15, 33)	18 (−5, 48)	22 (−3, 52)	43 (14, 79)	0.0005	11 (5, 17)
MV+BMI adjusted	0 (reference)	11 (−10, 37)	20 (−2, 48)	20 (−3, 48)	31 (6, 62)	0.005	8 (2, 14)

Note: EDIH and EDIP scores were adjusted for total energy intake using the residual method, with higher scores indicating hyperinsulinemic or proinflammatory dietary patterns, respectively.

All values were back-transformed (exp) because biomarker data were log-transformed (using natural logs) before analyses.

Multivariable-adjusted analyses controlled for age at blood draw, pack-years of smoking, physical activity, sex, education, marital status, race, PLCO study center, aspirin use, ibuprofen use, case-control status, family history of cancer, and additionally for BMI in separate models.

P value for linear trend was calculated using the continuous dietary score adjusted for all variables included in the multivariable-adjusted analyses.

and biomarkers were generally stronger among normal weight individuals for the inflammatory markers and stronger among obese individuals for c-peptide and insulin. Findings for EDIP in BMI subgroups were similar to those for EDIH. Supplementary Table S3 shows results for the smoking status subgroup analyses. The interaction between EDIH and smoking status was statistically significant for c-peptide and insulin with stronger results among never smokers. Findings for EDIP followed a similar trend, though interactions were not statistically significant.

Prostate cancer analysis

Participant characteristics for the prostate cancer analyses are presented in **Table 4**. The mean age of the participants was 62.5 ± 5.2 years, and 90.6% of the participants were European Americans. Similar to the biomarker sample, men with the most hyperinsulinemic or proinflammatory dietary patterns (quintiles 5) had a higher BMI and lower physical activity compared with men consuming the lowest insulinemic or most anti-inflammatory diets (quintiles 1). Distribution of food and nutrient intakes across quintiles of the dietary patterns is

Table 3. Multivariable-adjusted absolute mean concentrations (95% CI) of circulating biomarkers in quintiles of the dietary indices.

	EDIH score quintiles					
Statistical model	**Quintile 1**	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	***P* trend**
CRP (mg/L), $n = 2{,}954$	590	591	591	591	591	
Multivariable (MV)-adjusted	8.6 (7.3, 10.0)	9.2 (7.8, 10.7)	11.0 (9.4, 12.8)	11.1 (9.6, 13.0)	10.9 (9.3, 12.7)	<0.0001
MV+BMI adjusted	8.8 (7.5, 10.2)	9.4 (8.1, 10.9)	10.5 (9.0, 12.3)	10.6 (9.2, 12.3)	10.4 (9.0, 12.1)	0.001
Adiponectin (μg/mL), $n = 605$	121	121	121	121	121	
Multivariable (MV)-adjusted	20.3 (16.4, 25.2)	16.9 (13.6, 21.0)	13.9 (11.3, 17.2)	15.5 (12.4, 19.3)	14.5 (11.8, 17.9)	0.0005
MV+BMI adjusted	19.1 (15.5, 23.4)	16.4 (13.4, 20.2)	14.1 (11.5, 17.3)	15.7 (12.7, 19.3)	15.2 (12.5, 18.6)	0.009
IL6 (pg/mL), $n = 2{,}023$	404	405	405	405	404	
Multivariable (MV)-adjusted	0.7 (0.5, 0.8)	0.7 (0.5, 0.9)	0.8 (0.6, 1.0)	0.8 (0.7, 1.0)	0.7 (0.5, 0.8)	0.26
MV+BMI adjusted	0.7 (0.5, 0.8)	0.7 (0.5, 0.9)	0.8 (0.6, 1.0)	0.8 (0.7, 1.0)	0.7 (0.5, 0.8)	0.26
TNFα-R2 (ng/mL), $n = 3{,}516$	703	703	704	703	703	
Multivariable (MV)-adjusted	6.1 (5.8, 6.4)	6.3 (6.0, 6.6)	6.5 (6.2, 6.9)	6.5 (6.2, 6.9)	6.5 (6.2, 6.8)	0.0003
MV+BMI adjusted	6.1 (5.8, 6.4)	6.3 (6.0, 6.6)	6.5 (6.2, 6.8)	6.5 (6.2, 6.8)	6.4 (6.1, 6.7)	0.002
C-peptide (ng/mL), $n = 962$	192	193	192	193	192	
Multivariable (MV)-adjusted	1.8 (1.6, 2.1)	2.0 (1.7, 2.3)	2.0 (1.7, 2.3)	2.0 (1.7, 2.3)	2.3 (2.0, 2.7)	0.004
MV+BMI adjusted	1.8 (1.5, 2.1)	1.9 (1.6, 2.2)	1.9 (1.6, 2.2)	1.9 (1.6, 2.2)	2.1 (1.8, 2.5)	0.03
Insulin (pg/mL), $n = 961$	192	192	193	192	192	
Multivariable (MV)-adjusted	530 (427, 658)	610 (492, 757)	605 (489, 750)	699 (565, 865)	734 (594, 907)	0.001
MV+BMI adjusted	511 (417, 627)	579 (472, 710)	566 (462, 693)	642 (525, 785)	656 (536, 802)	0.01
	EDIP score quintiles					
	Quintile 1	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	***P* trend**
CRP (mg/L), $n = 2{,}954$	590	591	591	591	591	
Multivariable (MV)-adjusted	8.8 (7.5, 10.3)	9.9 (8.5, 11.6)	9.9 (8.5, 11.6)	10.5 (9.0, 12.2)	11.4 (9.8, 13.3)	0.006
MV+BMI adjusted	9.1 (7.8, 10.6)	10.1 (8.7, 11.8)	9.8 (8.4, 11.4)	10.1 (8.7, 11.7)	10.6 (9.1, 12.3)	0.16
Adiponectin (μg/mL), $n = 605$	121	121	121	121	121	
Multivariable (MV)-adjusted	19.4 (15.5, 24.2)	16.6 (13.3, 20.8)	15.8 (12.7, 19.6)	16.1 (12.9, 20.0)	14.0 (11.4, 17.3)	0.003
MV+BMI adjusted	18.0 (14.6, 22.2)	15.7 (12.7, 19.4)	16.0 (13.0, 19.6)	16.1 (13.1, 19.8)	14.9 (12.2, 18.1)	0.04
IL6 (pg/mL), $n = 2{,}023$	404	405	405	405	404	
Multivariable (MV)-adjusted	0.6 (0.5, 0.8)	0.7 (0.6, 0.9)	0.7 (0.5, 0.8)	0.8 (0.7, 1.0)	0.8 (0.6, 1.0)	0.04
MV+BMI adjusted	0.6 (0.5, 0.8)	0.7 (0.6, 0.9)	0.7 (0.5, 0.8)	0.8 (0.7, 1.1)	0.8 (0.6, 1.0)	0.04
TNFα-R2 (ng/mL), $n = 3{,}516$	703	703	704	703	703	
Multivariable (MV)-adjusted	6.0 (5.7, 6.4)	6.3 (6.0, 6.6)	6.4 (6.1, 6.8)	6.5 (6.2, 6.8)	6.6 (6.3, 7.0)	<0.0001
MV+BMI adjusted	6.1 (5.8, 6.4)	6.3 (6.0, 6.6)	6.4 (6.1, 6.7)	6.4 (6.1, 6.7)	6.5 (6.2, 6.9)	0.0005
C-peptide (ng/mL), $n = 962$	192	193	192	193	192	
Multivariable (MV)-adjusted	1.8 (1.5, 2.1)	2.0 (1.7, 2.4)	2.0 (1.7, 2.3)	2.2 (1.8, 2.5)	2.2 (1.9, 2.5)	0.002
MV+BMI adjusted	1.7 (1.5, 2.0)	2.0 (1.7, 2.3)	1.9 (1.7, 2.3)	2.1 (1.8, 2.4)	2.0 (1.7, 2.3)	0.02
Insulin (pg/mL), $n = 961$	192	192	193	192	192	
Multivariable (MV)-adjusted	535 (432, 663)	572 (460, 711)	634 (511, 785)	651 (525, 808)	764 (620, 940)	0.0005
MV+BMI adjusted	507 (414, 621)	562 (457, 690)	609 (497, 746)	606 (495, 743)	665 (545, 811)	0.005

Note: EDIH and EDIP scores were adjusted for total energy intake using the residual method, with higher scores indicating hyperinsulinemic or proinflammatory dietary patterns, respectively.

All values were back-transformed (exp) because biomarker data were log-transformed (using natural logs) before analyses.

Multivariable-adjusted analyses controlled for age at blood draw, pack-years of smoking, physical activity, sex, education, marital status, race, PLCO study center, aspirin use, ibuprofen use, case-control status, family history of cancer, and additionally for body weight in separate models.

P value for linear trend was calculated using the continuous dietary score adjusted for all variables included in the multivariable-adjusted analyses.

summarized in **Table 5**. The nutrient profile resulting from adhering to a low insulinemic or anti-inflammatory dietary pattern was characterized by higher intakes of total fiber, total carbohydrate, calcium and magnesium and lower intakes of total protein, total fat, especially saturated fat, and total cholesterol compared with those habitually consuming hyperinsulinemic or proinflammatory diets.

After a median 12.14 years of follow-up (5th, 95th percentile: 5.95, 15.23 years), 4,176 cases of total prostate cancer were diagnosed. Results describing the associations of the insulinemic and inflammatory potentials of the diet and risk of developing prostate cancer are presented in **Table 6**. Men classified in EDIH quintile 5 compared with 1 were at higher risk for total prostate cancer in multivariable-adjusted models: HR, 1.11; 95% CI, 1.01–1.23; *P* trend = 0.03, especially high-grade cancer: HR, 1.18; 95% CI, 1.02–1.37; *P* trend = 0.06. EDIP was not substantially associated with prostate cancer risk in all models.

Supplementary Tables S4, S5, and S6 show the multivariable-adjusted associations between the dietary patterns and prostate cancer risk (total, low-grade, and high-grade cancer) in categories of BMI, smoking status, and race/ethnicity, respectively.

Table 4. Characteristics of study participants in quintiles of the dietary indices in the prostate cancer sample.

Characteristic	Total population	EDIH score quintiles					EDIP score quintiles				
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Sample size	49,317	9,863	9,864	9,863	9,864	9,863	9,863	9,864	9,863	9,864	9,863
Age at baseline, years	62.5 ± 5.2	62.4 ± 5.2	62.8 ±5.3	62.8 ± 5.3	62.6 ±5.2	61.7 ± 5.1	61.8 ± 5.1	62.4 ± 5.2	62.7 ± 5.3	62.8 ± 5.3	62.6 ±5.3
BMI (kg/m^2), %	27.5 ± 4.1	26.5 ± 3.7	27.0 ± 3.7	27.3 ± 3.9	27.9 ± 4.0	28.8 ± 4.5	27.1 ± 3.9	27.3 ± 3.9	27.5 ± 4.0	27.6 ± 4.0	28.1 ± 4.4
Normal weight (18.5–<25)	26.0	35.3	29.1	26.4	21.9	17.4	29.2	27.3	25.6	25.0	23.0
Overweight (25–<30)	51.8	50.0	53.4	53.5	53.1	49.1	52.2	52.8	52.6	52.0	49.4
Obese (≥30)	22.2	14.7	17.5	20.1	25.0	33.6	18.5	20.0	21.7	23.0	27.6
Smoking status, %											
Current	37.6	33.6	36.5	39.4	41.6	37.1	29.1	32.5	36.3	41.9	48.2
Former	10.1	10.9	9.7	8.9	8.8	12.3	14.1	10.6	9.8	8.2	7.9
Never	52.3	55.6	53.9	51.8	49.7	50.6	56.8	56.9	53.9	50.0	43.9
Pack-years of smoking	23.7 ± 30.0	24.8 ± 30.0	23.7 ± 29.7	22.1 ± 29.0	21.9 ± 29.0	26.2 ± 32.4	29.0 ± 31.9	25.3 ± 29.6	23.9 ± 29.7	21.1 ± 28.7	19.3 ± 29.2
Vigorous activity, hours/week	2.8 ± 1.3	3.0 ± 1.3	2.9 ± 1.2	2.8 ± 1.2	2.7 ± 1.2	2.6 ± 1.3	2.8 ± 1.3	2.8 ± 1.2	2.8 ± 1.3	2.8 ± 1.2	2.7 ± 1.3
Number of supplements used	9 ± 8	10 ± 8	9 ± 8	9 ± 8	9 ± 8	9 ± 8	10 ± 7	10 ± 8	9 ± 8	9 ± 8	9 ± 8
Family history of cancer, %	52.1	51.1	52.3	51.6	52.9	52.4	51.9	52.6	51.6	51.9	52.3
Educational level, %											
<11 yrs	7.2	5.4	6.4	6.8	7.4	9.9	5.1	5.8	6.8	7.8	10.4
12 yrs or completed high school	18.3	13.7	16.1	18.3	20.9	22.6	14.9	15.7	18.2	20.2	22.6
Post high school training other than college	12.7	10.2	12.3	13.0	13.4	14.5	11.0	12.5	13.3	13.4	13.2
Some college	19.9	18.1	19.6	20.0	20.6	21.4	19.4	19.9	20.1	20.1	20.2
College graduate	19.5	22.1	20.8	19.7	18.7	16.3	21.5	21.3	19.9	18.4	16.6
Postgraduate	22.4	30.5	24.9	22.3	18.9	15.4	28.1	24.9	21.7	20.1	17.0
Aspirin use, %	51.8	53.1	53.1	51.9	50.3	50.7	53.8	53.4	53.1	50.3	48.6
Ibuprofen use, %	23.0	22.6	22.6	22.1	23.1	24.6	24.1	23.8	22.9	22.3	21.9
PSA history, %	46.7	49.1	48.5	47.7	46.5	41.4	47.3	48.4	47.3	47.2	43.0
White race, %	90.6	89.4	90.6	91.1	91.6	90.5	92.6	92.4	91.0	89.4	87.8

Note: Values are presented as mean ± SD for continuous variables and percentages for categorical variables. Dietary indices were adjusted for total energy intake.

Table 5. Means (5th, 95th percentiles) of the distribution of food and nutrient intakes across quintiles of the dietary indices.

	EDIH score quintiles			EDIP score quintiles		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Food/food groups, servings/week						
Red meat	4.1 (0.4, 10.2)	4.8 (0.9, 11.3)	10.0 (2.2, 23.3)	5.2 (0.7, 13.1)	5.4 (0.9, 13.5)	7.8 (1.2, 20.1)
Processed meat	3.0 (0.0, 9.2)	3.8 (0.3, 11.0)	14.1 (1.5, 36.9)	4.6 (0.3, 14.8)	5.0 (0.3, 16.1)	9.4 (0.4, 33.8)
Sugar-sweetened beverages	0.1 (0.0, 0.6)	0.2 (0.0, 0.8)	0.8 (0.0, 3.3)	0.2 (0.0, 0.6)	0.2 (0.0, 0.9)	0.8 (0.0, 3.8)
Tomatoes	2.8 (0.3, 8.2)	2.2 (0.2, 7.1)	3.1 (0.3, 9.6)	2.7 (0.3, 8.0)	2.2 (0.2, 7.0)	3.0 (0.2, 10.2)
Refined grains	10.3 (1.7, 28.6)	8.7 (1.6, 23.3)	11.4 (1.8, 29.1)	8.4 (1.5, 21.0)	8.9 (1.7, 21.7)	13.4 (2.2, 3.8)
Wholegrains[5]	29.2 (3.9, 70.0)	28.5 (4.8, 67.0)	20.2 (2.7, 49.8)	26.7 (3.2, 65.2)	27.4 (4.3, 65.7)	24.5 (3.3, 61.6)
Wine	5.0 (0.0, 15.5)	0.8 (0.0, 3.1)	0.5 (0.0, 3.1)	4.2 (0.0, 14.6)	1.1 (0.0, 6.2)	0.4 (0.0, 1.3)
Fruit juice	5.3 (0.0, 19.5)	3.9 (0.0, 9.4)	3.6 (0.0, 9.4)	4.5 (0.0, 14.5)	4.1 (0.0, 9.4)	3.8 (0.0, 9.4)
Dark-yellow vegetables	1.4 (0.0, 5.3)	0.9 (0.0, 3.3)	0.8 (0.0, 3.2)	1.3 (0.0, 5.3)	0.9 (0.0, 3.3)	0.9 (0.0, 3.2)
Green-leafy vegetables	26.3 (1.3, 74.8)	9.8 (0.6, 29.3)	9.6 (0.5, 30.1)	26.6 (1.3, 75.6)	10.4 (0.6, 30.0)	7.5 (0.3, 25.1)
Coffee or tea	45.6 (0.0, 110.4)	26.9 (0.0, 71.0)	23.2 (0.0, 71.0)	55.3 (0.3, 110.4)	29.6 (0.0, 66.5)	10.6 (0.0, 39.4)
Pizza	0.7 (0.0, 2.8)	0.7 (0.0, 2.1)	0.1 (0.0, 1.4)	0.7 (0.0, 2.8)	0.7 (0.0, 2.1)	0.2 (0.0, 1.4)
Nutrient intakes						
Total fiber, g/d	24.0 (10.0, 44.3)	16.9 (7.0, 30.9)	18.4 (7.5, 34.1)	20.7 (8.3, 38.7)	17.6 (7.1, 32.9)	20.3 (8.0, 37.8)
Total carbohydrate, g/d	289 (143, 491)	223 (106, 381)	250 (111, 443)	254 (120, 440)	231 (108, 399)	274 (124, 481)
Total protein, g/d	78.4 (38.0, 136.0)	66.4 (28.5, 121.1)	94.2 (42.7, 171.4)	77.1 (35.6, 135.7)	71.1 (31.2, 129.3)	87.9 (37.0, 164.6)
Total fat, g/d	73.2 (28.0, 144.5)	62.2 (23.1, 122.9)	93.8 (38.7, 177.7)	71.8 (27.7, 139.5)	67.7 (24.9, 133.5)	85.9 (31.1, 171.4)
Saturated fat, g/d	22.8 (7.8, 48.0)	20.1 (6.9, 41.2)	30.9 (12.2, 60.0)	22.6 (8.0, 46.0)	21.8 (7.5, 44.2)	28.4 (9.6, 58.6)
Total cholesterol, g/d	212 (66, 447)	208 (68, 425)	367 (139, 724)	236 (74, 501)	232 (73, 486)	305 (89, 661)
Dietary calcium, mg/d	939 (393, 1833)	753 (279, 1527)	843 (320, 1684)	849 (348, 1614)	773 (286, 1549)	925 (328, 1869)
Lycopene, mg/d	7.5 (1.9, 20.0)	6.2 (1.6, 16.8)	8.5 (2.0, 2.4.0)	7.3 (1.9, 18.9)	6.6 (1.7, 17.5)	8.9 (1.8, 25.0)
Dietary magnesium, mg/d	450 (259, 742)	318 (165, 531)	353 (166, 611)	437 (246, 715)	333 (170, 563)	344 (153, 607)

Note: Dietary indices were adjusted for total energy intake.

The interaction of diet with BMI was not statistically significant in EDIH and EDIP models. However, higher EDIP scores were associated with higher risk for total prostate cancer in obese participants; P trend = 0.007 (Supplementary Table S4). Also, the interaction of diet with smoking status was not statistically significant in both EDIH and EDIP models (Supplementary Table S5). The interaction of diet with race was also not statistically significant in EDIH and EDIP models (Supplementary Table S6).

Discussion

In cross-sectional analyses, we evaluated the association of two previously developed, mechanism-based dietary patterns (EDIH and EDIP), with concentrations of circulating biomarkers of insulin response and low-grade chronic systemic inflammation, and found that both dietary patterns were associated with concentrations of the biomarkers. These findings validate the constructs of the two dietary patterns in the PLCO cohort, i.e., insulin response for the EDIH and systemic inflammation for the EDIP. In addition, the finding that EDIH was predictive of concentrations of inflammation biomarkers while EDIP predicted concentrations of insulin response markers is in line with the interrelation between hyperinsulinemia and inflammation and the correlation between the two dietary indices, though each still retains unique characteristics. In the prospective analyses, we assessed the association between the two dietary patterns and risk of prostate cancer, and found that the EDIH score significantly predicted future risk of developing prostate cancer, especially high-grade cancer, whereas the EDIP score was not associated with prostate cancer risk.

The EDIH and EDIP scores were developed in the NHS and validated in NHS-II and HPFS, with the EDIP significantly predicting circulating concentrations of inflammatory markers (CRP, adiponectin, IL6, and TNFα-R2) and EDIH predicting circulating c-peptide concentrations (10, 11). The two scores have since been applied in other cohorts including the Women's Health Initiative in which the EDIP was associated with several more inflammatory markers (33) and the EDIH, associated with c-peptide (34). Our findings in the current study further show that these empirical hypothesis-oriented dietary patterns can be applied in other study populations with habitual dietary data. For the first time, we have examined the associations of both dietary patterns with the same biomarkers of inflammation and insulin response and found that both scores were associated with biomarkers in both pathways. This may not be surprising given that hyperinsulinemia and inflammation are two interrelated pathways. For example, hyperinsulinemia and chronic inflammation have been linked to obesity (35), which is also recognized as a state of low-grade chronic systemic inflammation and insulin resistance. Indeed, several circulating inflammatory and insulin response biomarkers are elevated in obesity (36–38). In addition, a qualitative synthesis of the food group components shows nine food groups common to both scores, including red meat, processed meat, non-dark fish, sugar-sweetened beverages, refined grains,

Table 6. Multivariable-adjusted HRs for the associations between empirical dietary index for hyperinsulinemia score and empirical dietary inflammatory pattern score and prostate cancer risk in the PLCO study.

Statistical model	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* trend	Per 1 SD increase in dietary score
			EDIH score quintiles				
Total prostate cancer							
Cases (n = 4,176)	799	864	824	885	804		
Person-years	117234.5	116365.1	115434.9	114840.4	111839		
Age and energy-adjusted HR (95% CI)	1 (Reference)	1.09 (0.99, 1.20)	1.05 (0.96, 1.16)	1.14 (1.04, 1.25)	1.09 (0.98, 1.20)	0.06	1.03 (1.00, 1.06)
Multivariable-adjusted HR (95% CI)	1 (Reference)	1.10 (1.00, 1.21)	1.06 (0.96, 1.17)	1.14 (1.04, 1.26)	1.11 (1.01, 1.23)	0.03	1.04 (1.01, 1.07)
Low-grade prostate cancer							
Cases (n = 2,151)	409	490	405	447	400		
Person-years	113931.5	113252.8	111917.5	111125.7	108525.8		
Age and energy-adjusted HR (95% CI)	1 (Reference)	1.21 (1.06, 1.38)	1.01 (0.88, 1.16)	1.12 (0.98, 1.29)	1.04 (0.91, 1.19)	0.26	1.03 (0.98, 1.07)
Multivariable-adjusted HR (95% CI)	1 (Reference)	1.22 (1.07, 1.39)	1.01 (0.88, 1.16)	1.11 (0.97, 1.28)	1.07 (0.93, 1.23)	0.15	1.03 (0.99, 1.08)
High-grade prostate cancer							
Cases (n = 1,980)	377	367	411	428	397		
Person-years	113843.5	112492.8	112310.1	111301.1	108895.2		
Age and energy-adjusted HR (95% CI)	1 (Reference)	0.98 (0.85, 1.13)	1.11 (0.97, 1.28)	1.17 (1.02, 1.35)	1.15 (1.00, 1.32)	0.10	1.04 (0.99, 1.09)
Multivariable-adjusted HR (95% CI)	1 (Reference)	1.00 (0.87, 1.16)	1.13 (0.98, 1.31)	1.20 (1.04, 1.38)	1.18 (1.02, 1.37)	0.06	1.05 (1.00, 1.10)
Advanced prostate cancer							
Cases (n = 286)	62	50	54	56	64		
Person-years	111080.7	109843.0	109246.5	108117.1	106087.0		
Age and energy-adjusted HR (95% CI)	1 (Reference)	0.83 (0.57, 1.21)	0.90 (0.63, 1.30)	0.93 (0.65, 1.33)	1.04 (0.73, 1.47)	0.75	1.02 (0.91, 1.14)
Multivariable-adjusted HR (95% CI)	1 (Reference)	0.87 (0.60, 1.26)	0.94 (0.65, 1.36)	0.97 (0.67, 1.41)	1.14 (0.79, 1.64)	0.43	1.05 (0.93, 1.19)
Lethal prostate cancer							
Cases (n = 270)	48	51	52	66	53		
Person-years	110928.7	109723.8	109126.6	108071.9	105868.2		
Age and energy-adjusted HR (95% CI)	1 (Reference)	1.06 (0.72, 1.57)	1.11 (0.75, 1.64)	1.46 (1.01, 2.12)	1.34 (0.91, 1.98)	0.11	1.11 (0.98, 1.25)
Multivariable-adjusted HR (95% CI)	1 (Reference)	1.05 (0.71, 1.56)	1.10 (0.74, 1.64)	1.45 (0.99, 2.13)	1.28 (0.86, 1.93)	0.19	1.09 (0.96, 1.24)
			EDIP score quintiles				
Total prostate cancer							
Cases (n = 4,176)	779	840	847	884	826		
Person-years	115715.6	115521.3	115553.2	114878.4	114045.3		
Age and energy-adjusted HR (95% CI)	1 (Reference)	1.07 (0.97, 1.18)	1.08 (0.98, 1.19)	1.14 (1.03, 1.25)	1.07 (0.97, 1.18)	0.08	1.03 (1.00, 1.06)
Multivariable-adjusted HR (95% CI)	1 (Reference)	1.07 (0.97, 1.18)	1.07 (0.97, 1.18)	1.11 (1.01, 1.22)	1.03 (0.93, 1.14)	0.35	1.02 (0.98, 1.05)
Low-grade prostate cancer							
Cases (n = 2,151)	406	442	428	448	427		
Person-years	112605.7	112132.5	111972.4	111292.3	110750.4		
Age and energy-adjusted HR (95% CI)	1 (Reference)	1.09 (0.96, 1.25)	1.06 (0.92, 1.21)	1.12 (0.98, 1.28)	1.07 (0.94, 1.23)	0.24	1.03 (0.98, 1.07)
Multivariable-adjusted HR (95% CI)	1 (Reference)	1.08 (0.95, 1.24)	1.04 (0.91, 1.20)	1.08 (0.94, 1.24)	1.02 (0.88, 1.17)	0.67	1.01 (0.97, 1.06)
High-grade prostate cancer							
Cases (n = 1,980)	362	396	406	425	391		
Person-years	112434.6	112121.1	112162.4	111341.4	110783.4		
Age and energy-adjusted HR (95% CI)	1 (Reference)	1.09 (0.94, 1.25)	1.11 (0.96, 1.28)	1.17 (1.02, 1.35)	1.09 (0.94, 1.26)	0.17	1.03 (0.99, 1.08)
Multivariable-adjusted HR (95% CI)	1 (Reference)	1.09 (0.94, 1.25)	1.10 (0.96, 1.27)	1.14 (0.99, 1.32)	1.06 (0.91, 1.23)	0.34	1.02 (0.98, 1.07)
Advanced prostate cancer							
Cases (n = 286)	57	49	67	53	60		
Person-years	109832.7	109108.4	109212.6	108220.4	108220.4		
Age and energy-adjusted HR (95% CI)	1 (Reference)	0.90 (0.61, 1.31)	1.24 (0.87, 1.76)	1.00 (0.69, 1.45)	1.13 (0.78, 1.62)	0.36	1.06 (0.94, 1.19)
Multivariable-adjusted HR (95% CI)	1 (Reference)	0.90 (0.61, 1.31)	1.23 (0.86, 1.76)	0.97 (0.66, 1.41)	1.07 (0.73, 1.57)	0.53	1.04 (0.92, 1.18)
Lethal prostate cancer							
Cases (n = 270)	53	56	58	49	54		
Person-years	109730.5	109031.6	108991.3	108109.2	107856.5		
Age and energy-adjusted HR (95% CI)	1 (Reference)	1.01 (0.69, 1.47)	1.03 (0.71, 1.50)	0.87 (0.59, 1.28)	0.98 (0.67, 1.44)	0.97	1.00 (0.89, 1.13)
Multivariable-adjusted HR (95% CI)	1 (Reference)	1.00 (0.69, 1.46)	1.01 (0.69, 1.47)	0.87 (0.59, 1.29)	0.95 (0.64, 1.42)	0.90	0.99 (0.87, 1.13)

Note: EDIH scores were adjusted for total energy intake using the residual method, with higher scores indicating hyperinsulinemic diets.
Gleason score 2–6 was used to define low-grade prostate cancer, 7–10 for high-grade cancer, advanced prostate cancer was defined using pathologic stage as stage T3, T4, N1, or M1 at diagnosis, or lymph node metastases, distant metastases, or prostate cancer death during follow-up, whereas lethal prostate cancer was defined as cases that metastasized to distant organs at diagnosis or over follow-up, or that caused prostate cancer death.
Multivariable-adjusted analyses included: age at enrollment, BMI, smoking status, physical activity, education, race, family history of cancer, use of PSA screening tests, PLCO study center, aspirin use, ibuprofen use, chronic disease comorbidity score, and occupation.
P value for linear trend was calculated using the continuous dietary score adjusted for all variables included in the multivariable-adjusted analyses.

wine, green-leafy vegetables, and coffee (10, 11). However, a Spearman correlation coefficient of 0.54 between EDIH and EDIP in the PLCO cohort suggests that the dietary patterns, though correlated, still retain unique features.

We found EDIH to be significantly associated with total prostate cancer and mainly with high-grade subtype. This may suggest that diet influences prostate cancer by insulinemic mechanisms. The peptide hormone insulin and other markers

such as c-peptide in this pathway are involved in the homeostatic regulation of glucose and energy metabolism (39). Insulin also has potent mitogenic and growth-stimulatory effects on body tissue including the prostate (40), and alterations in concentrations of these biomarkers eventually contribute to tumorigenesis (40). In addition, there is substantial evidence linking insulin resistance to increased risk of cancer development (40, 41). Though evidence on the causal role for hyperinsulinemia in prostate cancer development is limited and inconsistent, some studies (42, 43) found no association between insulin and prostate cancer risk, whereas several other studies (44–46) have found a strong positive relationship between insulin and insulinemic markers and higher prostate cancer risk. Also, most previous studies have focused on individual dietary factors such as carbohydrates in relation to prostate cancer development (47).

We did not find an association between dietary inflammatory potential and prostate cancer risk. Whereas inflammation at tissue level (9, 48) has been shown to increase risk of prostate cancer development, the degree to which systemic inflammation influences prostate cancer risk is inconclusive (49). Obesity, a state of low-grade chronic systemic inflammation, has been shown to increase risk mainly for fatal prostate cancer (50), though EDIP was not associated with fatal or lethal prostate cancer in the current study. Previous studies that have assessed dietary inflammatory potential using a literature-derived nutrient-based dietary inflammatory index have found positive associations between higher scores and prostate cancer risk (51, 52). However, the nutrient-based index is driven mainly by nutritional supplements, thus making it difficult to directly infer an effect of diet. Also, these previous studies used mainly the case–control study design with high potential for reverse causation.

The limitations of our study include the small sample size that could not allow for a thorough subgroup analysis. Measurement error in the dietary questionnaires is a known limitation; however, the dietary questionnaires were validated prior to use (28–30). Also, our participants were recruited from outpatient services of hospitals, thus the information obtained may not be representative of the general population. However, our study is a multicenter and multiethnic study conducted across ten states in the United States. Strengths of our study design include the use of several biomarkers for the construct validation of the dietary indices. Some of these biomarkers were not included in the original development of the scores, yet these scores were predictive of the biomarkers. These two empirical hypothesis-oriented dietary indices are a novel way of creating dietary patterns in nutritional epidemiology and have shown robust results with several health outcomes (4, 53, 54). Also, we were able to use a prospective design for the prostate cancer analysis.

In summary, the EDIH and EDIP scores predicted concentrations of biomarkers relevant to their respective constructs of dietary insulinemic and inflammatory potential. EDIH predicted future prostate cancer risk especially high-grade prostate cancer and may suggest a dietary pattern for prostate cancer prevention. Future studies are needed to confirm these findings and to study potential racial/ethnic differences using larger samples.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Ethics Approval and Consent to Participate

The study was approved by Institutional Review Boards at the NCI and the National Human Genome Research Institute in the United States. All participants provided written-informed consent.

Data Availability

The authors confirm that data used in developing this article are available upon reasonable request to the corresponding author. Raw data were generated by the PLCO trial and are available in the NCI database.

Authors' Contributions

D. Aroke: Conceptualization, data curation, software, formal analysis, methodology, writing-original draft. **E. Folefac:** Conceptualization, writing-review and editing. **N. Shi:** Data curation, writing-review and editing. **Q. Jin:** Data curation, writing-review and editing. **S.K. Clinton:** Writing-review and editing. **F.K. Tabung:** Conceptualization, data curation, formal analysis, supervision, funding acquisition, writing-review and editing.

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