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Diet-related inflammation and risk of prostate cancer in the California Men's Health Study

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ABSTRACT

Purpose: The purpose of the study was to examine the relationship between proinflammatory diet and prostate cancer risk.
Methods: Energy-adjusted Dietary Inflammatory Index (E-DII) scores were computed among 40,161 participants in the California Men's Health Study. Over 9.7 ± 3.8 years of follow-up, 2707 incident prostate cancer cases were diagnosed and categorized as low-, intermediate-, or high-risk, based on disease grade and stage. Accelerated failure-time models assessed time to diagnosis of prostate cancer. Cox proportional hazard models estimated hazard ratios (HR) and 95% confidence intervals (95% CI). Nonlinear effects of E-DII were modeled as third-order polynomials.
Results: Time to prostate cancer diagnosis did not differ by E-DII quartile. The HR for high-risk prostate cancer increased in the third E-DII quartile ($HR_{Q3\ vs.\ Q1} = 1.36$; 95% CI: 1.04–1.76), but not in the fourth ($HR_{Q4\ vs.\ Q1} = 0.99$; 95% CI: 0.74–1.32, $P_{trend} = .74$), suggesting a nonlinear dose–response. HR curves for prostate cancer increased exponentially above an E-DII threshold of ≈+3.0. HR curves for high-risk prostate cancer had a much steeper incline above an E-DII threshold of ≈+2.5. Curves were higher among Blacks and Whites relative to other races and among overweight or obese men. No relationship was observed between E-DII scores and intermediate- or low-risk disease.
Conclusions: Relationships between proinflammatory diet and prostate cancer risk may be nonlinear, with an increased risk above an E-DII threshold of ≈+2.5.

Introduction

In the United States, prostate cancer incidence and mortality rates vary by race and are the highest among African Americans (designated as Black) who tend to be diagnosed at younger ages and have more aggressive disease than their European American (White) counterparts [1]. In 2016, age-adjusted prostate cancer incidence rates in Blacks was 70% higher, and mortality was ≈2.5 times higher than in Whites [2], owing largely to more aggressive disease among Blacks.

Chronic inflammation within the prostate may play a role in prostate cancer initiation and progression [3, 4], and diet may

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modulate inflammation [5–7]. For instance, heterocyclic amines produced when cooking meat are associated with prostatic inflammation in animal models and with increased prostate cancer risk in epidemiologic studies [8, 9]. In contrast, phytochemicals from cruciferous vegetables (e.g., kale and cauliflower) exert antioxidant, proapoptotic, and antiproliferative effects in prostate cancer cells *in vitro* and in animal models [10]. Racial/ethnic minorities may have low fruit and vegetable consumption and sedentary lifestyles compared with non-Hispanic Whites [11, 12]. Such lifestyle patterns are associated with chronic, systemic inflammation [12, 13].

Previous studies of diet-associated inflammation and prostate cancer found stronger associations in Jamaican (mainly Black) and Iranian men (87% Persians and 13% Azerbaijanis) than in Italian, French, Canadian, or Mexican men [6,7,14–16]. Except for the French cohort, which consisted of 123 White men with incident prostate cancer [6], all of these were case–control studies. The relationships between diet-associated inflammation and prostate cancer have not been examined in prospective studies with large representation of racial/ethnic minorities.

The Dietary Inflammatory Index (DII) was developed to calculate the overall inflammatory potential of an individual's diet [17] based on review and ranking of 1943 articles focused on diet-related inflammation [17]. The DII scores are standardized against a range of actual food intakes in 11 populations globally, facilitating broad comparability among populations [17]. The DII has been shown to predict levels of inflammatory biomarkers including C-reactive protein (CRP) [18, 19], interleukin-6 (IL-6) [18, 20, 21], tumor necrosis factor alpha (TNF-α) (21), and homocysteine [22]. The first validation was conducted in the SEASONS study of 559 healthy adults, where DII scores were calculated from two different dietary assessment tools (up to 15 24-hour recalls and up to five 7-day dietary recalls over a period of 1 year). Higher DII scores were associated with values of high-sensitivity CRP >3 mg/L (odds ratio [OR] = 1.08; 95% confidence interval [CI]: 1.01–1.16, $P = .035$ for the 24-hour recalls; and OR = 1.10; 95% CI: 1.02–1.19, $P = .015$ for the 7-day dietary recalls, respectively) [18]. In analyses of data from 2567 postmenopausal women in the Women's Health Initiative, the DII was associated with IL-6 and TNF-α, with beta estimates comparing the highest DII quintile to the lowest DII quintile as follows: IL-6 1.26 (95% CI: 1.15–1.38, $P_{trend} < .0001$); TNF-α receptor 2: 81.43 (95% CI: 19.15–143.71, $P_{trend} = .004$) [21]. Analyses conducted in the Asklepios study of 2524 generally healthy adult Belgian adults showed significant positive associations between DII scores and the inflammatory markers IL-6 (>1.6 pg/mL) (OR = 1.19, 95% CI: 1.04–1.36) and homocysteine (>15 μmol/L) (OR = 1.56, 95% CI: 1.25–1.94) [22]. A higher (more proinflammatory) DII score has been associated with increased risk of asthma [20], cardiovascular disease [23], and cancers of the colorectum [24–33], pancreas [34, 35], esophagus [36–39].

Previous studies of the DII and prostate cancer have been conducted in racially or ethnically homogeneous populations (essentially all Black, White, Iranian, or Mexican) [6,7,14–16,40]. Using data from a prospective cohort study in California, this study tested the hypothesis that men with higher (i.e., proinflammatory) energy-adjusted DII (E-DII) scores had elevated prostate cancer risk and a higher risk of more aggressive prostate cancer, relative to those with anti-inflammatory diets. It was further hypothesized that these associations would be stronger among Blacks compared with other races, as was observed previously [7].

Methods

Study population

The California Men's Health Study (CMHS) is a large multiethnic cohort of US members of Kaiser Permanente (KP), an integrated health care provider covering residents of Northern and Southern California. In 2002–2003, the CMHS recruited 43,202 men aged 45–69 years from the Northern California region; 35% of whom were from minority populations, including Chinese, Hispanics, and Blacks [41]. Information on participants' demographics, health status, family history of prostate cancer, medication and supplement use, and prostate cancer risk factors (e.g., diet, physical activity, and sleep) were collected at enrollment via mailed questionnaires [41]. Return of the questionnaire in the mail by the participant constituted an informed consent. The 2014 follow-up rate was 81.2%. This study was approved by the Institutional Review Boards of KP Northern California and the University of South Carolina.

The study population comprised CMHS participants with active KP membership for at least 1 year before enrollment. Individuals were excluded if they had any cancer at enrollment (except nonmelanoma skin cancer, $n = 1363$), were missing information on race/ethnicity ($n = 346$), or had implausible total daily energy intake (<500 kcal or >6000 kcal, $n = 958$). Participants diagnosed with prostate cancer after enrollment but missing information on cancer stage were excluded from analyses requiring that information ($n = 65$).

Prostate cancer ascertainment

Ascertainment of incident prostate cancer cases was performed via linkage to the KP Northern California Cancer Registry, which ascertains and reports all cases according to standards established by the National Cancer Institute's Surveillance, Epidemiology, and End Result Program.

Prostate cancer was categorized into three groups using the updated (2010) version of the standard prostate cancer staging system endorsed by the American Joint Committee on Cancer/International Union Against Cancer [42]. The high-risk prostate cancer group included men with clinically localized high-risk prostate cancer and advanced, very high-risk prostate cancer (≥T3a or prostate-specific antigen (PSA) > 20 ng/mL or Gleason score of 8–10). The clinically localized, intermediate-risk group consisted of men with T2b-T2c, or T1-T2a and PSA10-20, or T1-T2a and a Gleason score of 7. All other cases were in the clinically localized, low-risk prostate cancer group.

Dietary assessment

Usual diet during the previous year was assessed at baseline from a self-administered semiquantitative food frequency questionnaire (FFQ) using a version of the Women's Health Initiative FFQ modified for use in men [43, 44]. Nutrient content was calculated using the Nutrition Data Systems for Research software (NDS-R; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). The FFQ provided information on 27 food parameters needed to compute individual DII scores (carbohydrate, protein, total fat, alcohol, fiber, cholesterol, saturated fat, monounsaturated fatty acid, polyunsaturated fatty acids , omega-3, omega-6, trans-fat, niacin, thiamin, riboflavin, B12, B6, iron, magnesium, zinc, selenium, vitamin A, vitamin C, vitamin D, vitamin-E, folic acid, and beta-carotene) described previously [17] (Supplementary File). Negative E-DII scores are associated with anti-inflammatory potential, whereas positive scores indicate more pro-inflammatory potential [17].

Confounder assessment

Information on potential confounders was collected at baseline via questionnaire and medical record review. Physical activity was

Table 1
Participants' characteristics (*n*, %) by quartiles of energy-adjusted dietary inflammatory index (E-DII) score at baseline, California Men's Health Study, 2002–2014

Characteristic	Q1: −6.1940 to ≤−3.3597 (the most anti-inflammatory) *n* = 10,042	Q2: −3.3597 to ≤−2.0313, *n* = 10,040	Q3: −2.0313 to ≤−0.5517, *n* = 10,040	Q4: −0.5517 to 4.8927 (the most proinflammatory), *n* = 10,039
Age at baseline (y)				
44–50	1649 (16.4)	1884 (18.8)	2122 (21.1)	2447 (24.4)
51–55	2006 (20.0)	2173 (21.6)	2236 (22.3)	2363 (24.5)
56–60	2223 (22.1)	2132 (21.2)	2126 (21.2)	2136 (21.3)
61–65	2312 (23.1)	2050 (20.4)	1936 (19.3)	1731 (17.2)
66–70	1852 (18.4)	1801 (18.0)	1620 (16.1)	1362 (13.6)
Race				
White	6989 (69.6)	6555 (65.3)	6380 (63.6)	6212 (61.9)
Black	429 (4.3)	483 (4.8)	606 (6.0)	801 (8.0)
Asian	973 (9.7)	1128 (11.2)	923 (9.2)	852 (8.5)
Hispanic	793 (7.9)	973 (9.7)	1148 (11.4)	1121 (11.2)
Multiethnic/other	858 (8.5)	901 (9.0)	983 (9.8)	1053 (10.5)
Body mass index (kg/m^2)				
Normal, <25	3388 (33.7)	2876 (28.7)	2488 (24.8)	2191 (21.8)
Overweight, 25 to <30	4572 (45.5)	4694 (46.7)	4750 (47.3)	4442 (44.3)
Obese, ≥30	1946 (19.4)	2329 (23.2)	2660 (26.5)	3210 (32.0)
Education				
High school, equivalent or less	1510 (15.0)	1934 (12.3)	2349 (23.4)	2822 (28.1)
Vocational/tech school	2451 (24.4)	2766 (27.6)	2977 (29.7)	3393 (33.8)
Some college, associate or bachelor degree	2267 (22.6)	2304 (22.9)	2304 (22.9)	2019 (20.1)
Graduate/professional school	3776 (37.6)	2996 (29.8)	2377 (23.7)	1753 (14.5)
Missing	38 (0.4)	40 (0.4)	33 (0.3)	52 (0.5)
Income ($ per year)				
<40,000	1421 (14.1)	1630 (16.2)	1850 (18.4)	2112 (21.0)
40–59,000	1565 (15.6)	1772 (17.7)	1864 (18.6)	2020 (20.1)
60–80,000	1649 (16.4)	1784 (17.8)	1861 (18.5)	1865 (18.6)
80–100,000	1382 (13.8)	1433 (14.3)	1352 (13.5)	1370 (13.7)
>100,000	3616 (36.0)	3026 (30.1)	2745 (27.3)	2296 (22.9)
Missing	409 (4.1)	395 (3.9)	368 (3.7)	376 (3.7)
Marital status				
Married/living with a partner	8463 (84.3)	8322 (82.9)	8234 (82.0)	7871 (78.4)
Single	1539 (15.3)	1699 (16.9)	1776 (17.7)	2129 (21.2)
Missing	40 (0.4)	19 (0.2)	30 (0.3)	39 (0.4)
Total physical activity (MET-min/wk)				
0–359	1401 (13.9)	2125 (21.2)	2744 (27.3)	3749 (37.3)
360–1102	2229 (22.2)	2504 (24.9)	2649 (26.4)	2635 (26.2)
1103–2201	2743 (27.3)	2638 (26.3)	2488 (24.8)	2144 (21.4)
>2202	3653 (36.4)	2753 (27.4)	2137 (21.3)	1484 (14.8)
Missing	16 (0.2)	20 (0.2)	22 (0.2)	27 (0.3)
Sleep duration (h/d)				
≤6	2115 (21.1)	2209 (22.0)	2235 (22.3)	2271 (22.6)
7	2959 (29.5)	2733 (27.2)	2574 (25.6)	2278 (22.7)
≥8	2284 (22.7)	2085 (20.8)	2055 (20.5)	1873 (18.7)
Missing	2684 (26.7)	3013 (30.0)	3176 (31.6)	3617 (36.3)
NSAID regular* use				
No	7032 (70.0)	6851 (68.2)	6646 (66.2)	6556 (65.3)
Yes	1268 (12.6)	1330 (13.3)	1478 (14.7)	1607 (16.0)
Missing	1742 (17.4)	1859 (18.5)	1916 (19.1)	1876 (18.7)
Multivitamin regular* use				
No	4392 (43.7)	5022 (50.0)	5430 (54.1)	6034 (60.1)
Yes	5650 (56.3)	5018 (50.0)	4610 (45.9)	4005 (39.9)
Smoking status				
Nonsmoker	4626 (46.1)	4471 (44.5)	4150 (41.3)	3692 (36.8)
Former smoker	4666 (46.5)	4544 (45.3)	4601 (45.8)	4430 (44.1)
Current smoker	511 (5.1)	782 (7.8)	1061 (10.6)	1624 (16.2)
Missing	239 (2.4)	243 (2.4)	228 (2.3)	293 (2.9)
Diabetes				
No	8894 (88.6)	8805 (87.7)	8753 (87.2)	8883 (88.5)
Yes	1148 (11.4)	1235 (12.3)	1287 (12.8)	1156 (11.5)
Benign prostatic hyperplasia				
No	7459 (74.3)	7548 (75.2)	7691 (76.6)	7899 (78.7)
Yes	2201 (21.9)	2075 (20.7)	1897 (18.9)	1705 (17.0)
Missing	382 (3.8)	417 (4.2)	452 (4.5)	435 (4.3)
Family history of prostate cancer†				
No	8792 (87.6)	8811 (87.8)	8737 (87.0)	8799 (87.6)
Yes	1250 (12.4)	1229 (12.2)	1303 (13.0)	1240 (12.4)

NSAID = nonsteroidal anti-inflammatory drug.
* Use 3–4 times per week.
† Father or brother had prostate cancer.

Table 2
Relationships between quartiles of energy-density DII and incidence of prostate cancer of any stage, California Men's Health Study, 2002–2014

Participant categories		Q1: −6.1940 to ≤−3.3597	Q2: −3.3598 to ≤−2.0313	Q3: −2.0314 to ≤−0.5517	Q4: −0.5518 to 4.8927
All participants	*N* with prostate cancer	636	609	616	514
	AF (95% CI)*	1.00 (Ref.)	1.00 (0.90–1.11)	0.96 (0.86–1.06)	1.07 (0.95–1.20)
Men diagnosed with prostate cancer during first 3 y of follow-up removed	*N* with prostate cancer	456	441	483	372
	AF (95% CI)*	1.00 (Ref.)	0.99 (0.92–1.07)	0.92 (0.85–0.99)	1.03 (0.95–1.11)
Stratified by race					
White	*N* with prostate cancer	481	423	418	315
	AF (95% CI)*	1.00 (Ref.)	1.02 (0.90–1.16)	0.96 (0.85–1.09)	1.16 (1.01–1.34)
Black	*N* with prostate cancer	35	44	73	74
	AF (95% CI)*	1.00 (Ref.)	0.89 (0.58–1.36)	0.65 (0.44–0.96)	0.75 (0.50–1.11)
Asian	*N* with prostate cancer	41	52	38	30
	AF (95% CI)*	1.00 (Ref.)	0.92 (0.60–1.40)	0.95 (0.60–1.51)	0.99 (0.61–1.62)
Hispanic	*N* with prostate cancer	45	48	45	45
	AF (95% CI)*	1.00 (Ref.)	1.09 (0.75–1.59)	1.36 (0.93–1.99)	1.22 (0.83–1.80)
Multiethnic/other	*N* with prostate cancer	34	42	42	50
	AF (95% CI)*	1.00 (Ref.)	0.79 (0.51–1.22)	0.80 (0.52–1.23)	0.68 (0.44–1.04)

Accelerated failure time models with log-logistic distribution were used to estimate parameters.
AF = acceleration factor; CI = confidence interval; DII = Dietary Inflammatory Index; Ref. = reference group.
* Adjusted for age (in 5-year intervals), race, sleep, benign prostatic hyperplasia, body mass index, prostate cancer family history, diabetes, and smoking status.

assessed using questions adapted from the Coronary Artery Risk Development in Young Adults Physical Activity History [45]. Analysis of frequency, duration, and intensity of recreational, household, and occupational activities yielded a total physical activity estimate in MET-hours per week [41]. The following variables were tested as potential confounders for inclusion in statistical models: race/ethnicity; 5-year intervals of age at baseline; body mass index (BMI = self-reported weight (kg)/height $(m)^2$); education; smoking status; alcohol; income; regular use of nonsteroidal anti-inflammatory drugs; regular multivitamin use; sleep duration; total physical activity; history of diabetes; family history of prostate cancer; and personal history of benign prostatic hyperplasia.

Statistical analysis

Follow-up time was censored at prostate cancer diagnosis, death, gap in KP membership exceeding 90 days, or the end of the study (December 31, 2014), whichever came first. Quartiles of E-DII distribution across all participants were used to define categories. A manual backward selection procedure was used to identify covariates for inclusion in multivariable models. Variables were retained in the final statistical models if their exclusion resulted in a change in the effect estimate for E-DII scores by ≥10% or if they were statistically significant ($\alpha < 0.05$). The proportional hazards assumption was tested using the negative logarithm of cumulative hazard estimators and cumulative Martingale residuals, as appropriate. Effect modification was tested using a Likelihood Ratio Test (LRT) or Wald test, as appropriate, and by stratification on levels of the effect modifier. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and R (The R Foundation for Statistical Computing, version 3.5.0.). Significance was set at $\alpha = 0.05$ (two-tailed).

In analyses of relationships between E-DII score and total (any stage) prostate cancer, the proportional hazards assumption did not hold; thus, the parametric accelerated failure time model was used with a log-logistic distribution (PROC LIFEREG in SAS) [46]. The log-logistic distribution was reasonable based on the residuals plot, and the acceleration factor was presented with 95% CIs.

Cox proportional hazards models were used to assess the relationships between E-DII score and high-, intermediate-, or low-risk prostate cancer using the PHREG procedure in SAS. For linear trend tests, the median of each E-DII quartile was included in statistical models as a continuous variable, with adjustment for the same confounders included in previous analyses. Sensitivity analyses were conducted to assess the possibility of reverse causality by excluding cases diagnosed during the first 3 years of follow-up.

Nonlinear effects of E-DII scores were modeled among the subset of participants with follow-up time of 4 years or more using the "simPH" package in R [47]. A third-order polynomial of E-DII was modeled in the Cox Proportional Hazards model, with adjustment for these confounders: race, BMI, family history of prostate cancer in a first-degree relative, physical activity, education, diabetes, smoking, age, and benign prostatic hyperplasia. The central 95% probability interval of HR curves was obtained through simulations using "coxsimPoly" and plotted using "simGG" functions. Analyses stratified by race and BMI were further conducted in a similar manner. The same approach was used to evaluate nonlinear effects of E-DII scores on high-risk prostate cancer incidence overall and stratified by race.

Results

The population consisted of 40,161 men with mean follow-up of 9.7 years (SD = 3.83), including 2707 men diagnosed with incident prostate cancer.

Participants' baseline characteristics are presented in Table 1 by E-DII quartile. Compared with the first (most anti-inflammatory) quartile of E-DII, men in the fourth (most proinflammatory) quartile were younger, had higher BMI, and had lower educational attainment and income.

There was no statistically significant difference in time to diagnosis of incident prostate cancer between men by E-DII quartile, after adjustment for confounders (Table 2). Men in the highest quartile of E-DII had an acceleration factor of 1.07 (95% CI: 0.95–1.20) relative to those in the lowest quartile. Exclusion of men diagnosed within 3 years of follow-up did not alter the results (Table 2). In race-stratified analyses, White men in the fourth E-DII quartile had 1.16-times longer time to diagnosis (95% CI: 1.01–1.34) relative to the first quartile. Among Black men in the third E-DII quartile, time to prostate cancer diagnosis was 0.65 as long as those in the first quartile (95% CI: 0.44–0.96); however, no relationship was detected in the fourth quartile.

Among participants with follow-up time of 4 years or more, the effect of E-DII score was nonlinear (Fig. 1A–C). When E-DII scores were less than −3.5, HRs were less than 1.0; when E-DII scores were

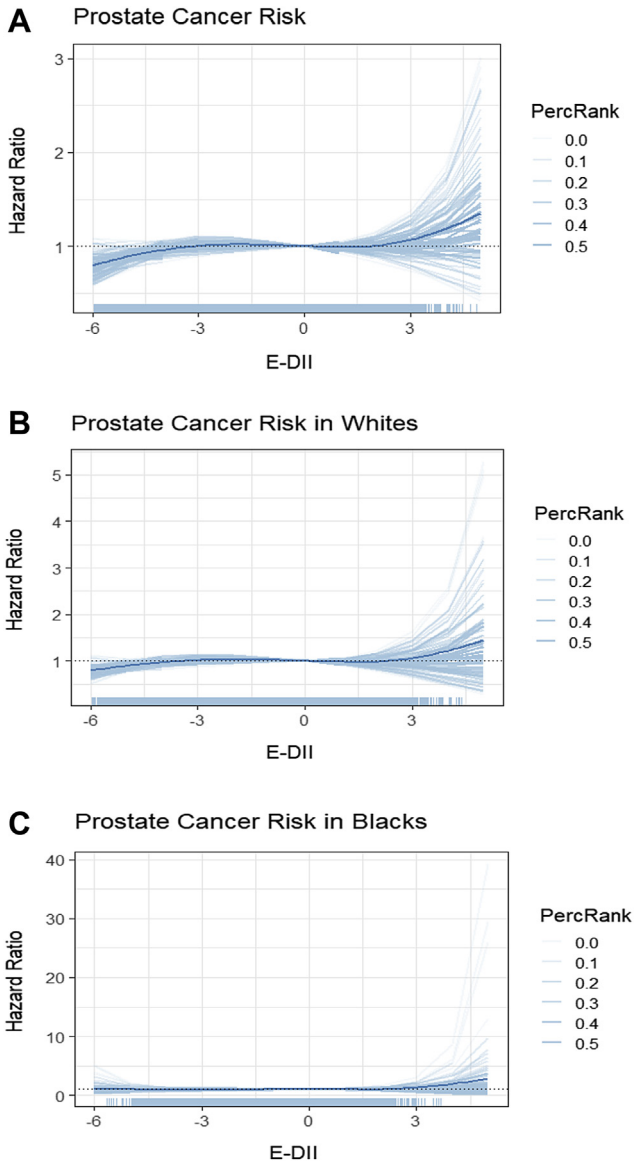

Fig. 1. Relationships between E-DII score and risk of prostate cancer (any stage) among participants with follow-up time ≥4 y: (A) in all participants, (B) in Whites, (C) in Blacks. E-DII = Energy-adjusted Dietary Inflammatory Index.

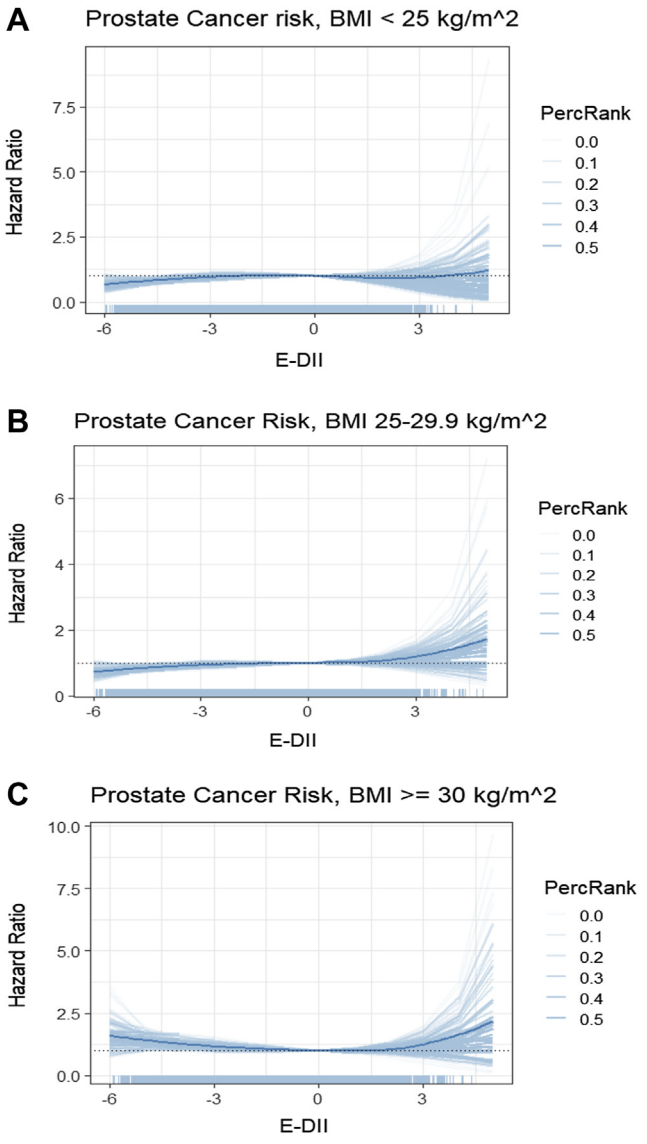

Fig. 2. Relationships between E-DII score and risk of prostate cancer (any stage) among participants with follow-up time ≥4 y by BMI: (A) BMI < 25 kg/m^2, (B) BMI 25–29.9 kg/m^2, (C) BMI ≥ 30 kg/m^2. E-DII = Energy-adjusted Dietary Inflammatory Index; BMI = body mass index.

between −3.5 and ≈+2.5, HRs were flat at 1.0; and when E-DII scores were above a threshold of +2.5, HRs began to increase exponentially (Fig. 1A). Prostate cancer risk varied by race (interaction term E-DII × race: Wald $P_{interaction}$ = .18, LRT P = .01). The HR curve among Whites had a shape similar to the one for all participants, with lower and upper cut-off points of E-DII scores ≈−4.0 and +3.0, respectively (Fig. 1A–C). There was only one cut-off point among Blacks at ≈+3.0, and the HR curve was higher relative to curves for all men and other strata (Fig. 1B). HR curves in other race strata were less informative (not shown). HR curves for E-DII also varied by levels of BMI (interaction term E-DII × BMI: Wald $P_{interaction}$ = .03, LRT P = .01; Fig. 2). Among men of normal weight (BMI < 25.0 kg/m^2), the HR curve was essentially a flat line at ≈+1.0 (Fig. 2A). Among overweight (25.0–29.9 kg/m^2) and obese men (≥30.0 kg/m^2), HRs were <1.0 at E-DII scores <−3.0 and increased above an E-DII threshold of +2.5 to +3.0 (Fig. 2B and C).

HRs for high-risk prostate cancer increased by 27% and 36%, respectively, in the second and third E-DII quartiles, although there was no association between the highest and the lowest E-DII quartiles (Table 3). Relationships between E-DII score and high-risk prostate cancer were modified by race (LRT P = .0002, Wald $P_{interaction}$ = .41). In race-stratified analyses, high-risk prostate cancer among Blacks increased across E-DII quartiles and was elevated by nearly fourfold among those in the third E-DII quartile ($HR_{Q3\ vs.\ Q1}$ = 3.77; 95% CI: 1.29–11.06). Among participants in the multiethnic/other category, there was a 23% increase in high-risk prostate cancer per unit E-DII score (HR = 1.23; 95%: 1.03–1.48; Table 3). After exclusion of cases diagnosed during the first 3 years of follow-up, the risk of high-risk prostate cancer appeared to be the highest in the third quartile (HR = 1.35; 95% CI: 1.01–1.81). No relationship was observed between E-DII and the risk of intermediate- or low-risk prostate cancer (Table 3).

Analyses of the nonlinear effects of E-DII indicated that adjusted HRs for high-risk prostate cancer increased above the threshold E-DII values +2.0 to +2.5 (Fig. 3A). Similar patterns were observed for Whites and Blacks separately (Fig. 3B and C), and negligible increases in HRs were noted among Asians, Hispanics, and Other race groups at the E-DII levels ≥+3.0 (not shown).

Table 3
Relationships between energy-adjusted Dietary Inflammatory Index score and prostate cancer by levels of risk, California Men's Health Study 2002–2014

	Q1: −6.1940 to ≤−3.3597 (anti-inflammatory)	Q2: −3.3598 to ≤−2.0313	Q3: −2.0314 to ≤−0.5517	Q4: −0.5518 to ≤4.8927 (proinflammatory)	*P* value for tend
High-risk prostate cancer					
N with prostate cancer	100	123	126	88	
Age-adjusted HR (95% CI)	1.00 (Ref.)	1.28 (0.98–1.67)	1.39 (1.07–1.80)	1.04 (0.78–1.38)	.97
HR (95% CI)*	1.00 (Ref.)	1.27 (0.98–1.66)	1.36 (1.04–1.76)	0.99 (0.74–1.32)	.74
Cases diagnosed during first 3 y removed					
N with prostate cancer	83	94	103	67	
HR (95% CI)*	1.00 (Ref.)	1.19 (0.88–1.59)	1.35 (1.01–1.81)	0.93 (0.67–1.28)	.99
Stratified by race*					
Whites (*n*)	73	86	69	46	
HR (95% CI)*	1.00 (Ref.)	1.29 (0.95–1.76)	1.12 (0.81–1.56)	0.80 (0.55–1.16)	NA
Blacks (*n*)	4	11	20	15	
HR (95% CI)*	1.00 (Ref.)	2.43 (0.77–7.64)	3.77 (1.29–11.06)	2.29 (0.76–6.94)	NA
Asians (*n*)	10	11	13	6	
HR (95% CI)*	1.00 (Ref.)	0.97 (0.41–2.30)	1.51 (0.66–3.46)	0.81 (0.30–2.24)	NA
Hispanics (*n*)	9	9	13	11	
HR (95% CI)*	1.00 (Ref.)	0.91 (0.36–2.28)	1.16 (0.49–2.72)	1.11 (0.46–2.70)	NA
Multiethnic/others (*n*)	4	6	9	11	
HR (95% CI)*	1.00 (Ref.)	1.68 (0.47–5.97)	2.97 (0.94–9.34)	2.94 (0.92–9.43)	NA
Intermediate-risk prostate cancer					
N with prostate cancer	237	242	239	201	
Age adjusted, HR (95% CI)	1.00 (Ref.)	1.06 (0.88–1.26)	1.08 (0.90–1.30)	0.96 (0.79–1.16)	.70
HR (95% CI)†	1.00 (Ref.)	1.05 (0.88–1.26)	1.06 (0.88–1.26)	0.91 (0.76–1.10)	.36
Cases diagnosed during first 3 y removed					
N with prostate cancer	180	174	195	144	
HR (95% CI)†	1.00 (Ref.)	1.01 (0.82–1.24)	1.15 (0.94–1.41)	0.89 (0.71–1.11)	.53
Low-risk prostate cancer					
N with prostate cancer	315	289	274	251	
Age adjusted, HR (95% CI)	1.00 (Ref.)	0.95 (0.81–1.11)	0.93 (0.79–1.09)	0.17 (0.75–1.05)	.17
HR (95% CI)‡	1.00 (Ref.)	0.89 (0.76–1.05)	0.92 (0.78–1.09)	0.89 (0.75–1.06)	.24
Cases diagnosed during first 3 y removed					
N with prostate cancer	194	181	186	167	
Age adjusted, HR (95% CI)‡	1.00 (Ref.)	0.96 (078–1.17)	1.02 (0.84–1.25)	0.96 (0.78–1.18)	.86
HR (95% CI)	1.00 (Ref.)	0.97 (0.81–1.21)	1.05 (0.86–1.29)	1.01 (0.82–1.25)	.78

Cox proportional hazards models were used to calculate parameters.
CI = confidence interval; HR = hazard ratio; Ref. = reference group.
* Adjusted for race and BPH; sleep duration and age (≤55, 55–65, >65 y) are in strata statement.
† Adjusted for race, benign prostatic hyperplasia, family history of prostate cancer; sleep duration (categorical) and age (≤55, 55–65, >65 y) are in strata statement.
‡ Adjusted for race, benign prostatic hyperplasia, body mass index, family history of prostate cancer, and smoking; sleep duration (categorical) and age (≤55, 55–65, >65 y) are in strata statement.

Discussion

This is the first multiethnic prospective study that analyzed relationships between proinflammatory diet, expressed using the E-DII, and prostate cancer risk across levels of disease severity. When all cases were considered in the aggregate over 0–12 years of follow-up, the E-DII was not associated with time to diagnosis of prostate cancer. When only high-risk prostate cancer was examined, an increased risk with increasing E-DII was observed, although it was the highest in the third, rather than the fourth, quartile, suggesting a possible nonlinear dose–response pattern. When the dose–response relationship between E-DII and prostate cancer risk was modeled using a third-order polynomial (cubic splines) in a subset of participants who were followed up for 4 years or more, the effect of E-DII also was nonlinear. Below the E-DII threshold of −4.0 (anti-inflammatory) risk of total prostate cancer decreased and above the threshold of ~+3.0, prostate cancer risk increased exponentially. Slight variations in the E-DII threshold and the increases in the HRs were observed among different strata of race and BMI. The pattern of the nonlinear relationship between E-DII score and high-risk prostate cancer resembled the one observed among men at all stages of prostate cancer with a follow-up 4 years or more. The risk above the E-DII threshold of ≈+2.5, however, was higher among men with high-risk prostate cancer relative to those with prostate cancer of any stage. The E-DII was not associated with intermediate- or low-risk prostate cancer.

To date, six studies have examined the relationship between DII scores and prostate cancer [6,7,14–16,40], including four case–control studies [7, 14, 16, 40]. In the Jamaican study, men in the highest DII quartile were 2.4 times more likely to have prostate cancer relative to those in the least inflammatory first quartile [7]. A prospective study in France found that men in the highest DII quartile had prostate cancer risks 2.1 times higher than those with anti-inflammatory diets [6]. Two relatively small case–control studies conducted in Canada [15] and Iran [40], and a large case-control study in Italy [14], also observed increased risk of prostate cancer associated with a higher DII score.

The lack of association between E-DII and total prostate cancer before stratification by race in the present study may be attributed to several factors. The dose–response analysis among men followed-up for 4 years or more suggested that diet may have a nonlinear effect with two thresholds. Anti-inflammatory diets below E-DII threshold of ≈−4.0 had protective effects, and highly proinflammatory diets with E-DII values above a threshold of ≈+3.0 were associated with increased prostate cancer risks although the associations were modest. The relationship may vary by both disease aggressiveness and race. In the Jamaican study, more than 50% of prostate cancer cases were high grade (Gleason score ≥7), and all participants were of African descent [7, 48]. In the present study, high-risk prostate cancer cases represented only 18% of cases, and Black men represented only 6% of the study population. Plots suggest that the increase in risk may be driven by strata

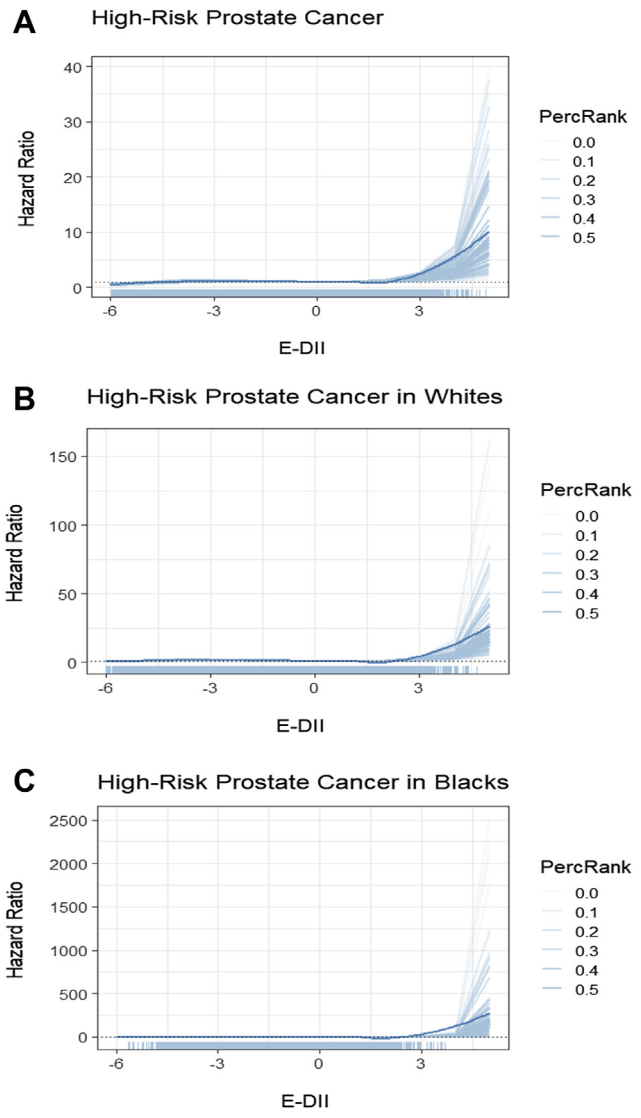

Fig. 3. Relationships between E-DII score and risk of high-risk prostate cancer: (A) All participants, (B) among Whites, (C) among Blacks. E-DII = Energy-adjusted Dietary Inflammatory Index.

of risk among Blacks and Whites. However, extended time to diagnosis of total prostate cancer among Whites in the fourth (most proinflammatory) E-DII quartile relative to the most anti-inflammatory first quartile contradicts the dose–response curve. Among Blacks, time to prostate cancer diagnosis was accelerated among those in the third quartile relative to the first quartile but not in the fourth. It is plausible that these differences in time to prostate cancer diagnosis observed between quartiles within each race stratum may have been because of the arbitrary selection of cut-off points in that analysis.

In race-stratified analyses, the relationship between E-DII and high-risk prostate cancer was the strongest among Blacks and those in the "multiethnic/other" race group (this latter group could have included those of mixed race with some African admixture). The risk estimates for high-risk prostate cancer among Blacks were similar in magnitude to prostate cancer risk in the Jamaican study [7]. Dose–response analyses performed using cubic splines suggested that high-risk prostate cancer increased with consumption of proinflammatory diets above an E-DII threshold of +2.5 to +3.0, and that risks may be elevated among both Blacks and Whites relative to other races; however, those analyses had relatively few prostate cancer cases above the E-DII threshold of +2.5 and should be interpreted with caution. It should be noted that in our previous work in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data to determine cut-off points for detecting high-risk prostate cancer using multiple PSA tests, we found a similar nonlinear relationship, that was especially prominent in Blacks [49, 50]. How this relates to the current work on inflammation is unclear, but it has been known for some time that prostate cancer growth and progression often present as nonlinear phenomena [51–53].

Among Italian men, E-DII–associated prostate cancer risks were similar in both the third ($OR_{Quartile3v.1} = 1.32$, 95% CI: 1.03–1.69) and fourth E-DII quartiles ($OR_{Quartile4v.1} = 1.33$; 95% CI: 1.01–1.76) [14]. This suggests a nonlinear relationship between diet and prostate cancer and possibly a threshold effect. The French study investigated dose–response between DII scores and prostate cancer using restricted cubic splines [6]. Men with DII ≥ -1.0 had a 2.3-fold increased prostate cancer risk relative to those with DII < -1.0 (HR = 2.31; 95% CI: 1.35–3.95; $P = .002$) [6]. Increased prostate cancer risk among men in other studies also was observed for DII scores ≥ -1.0 [6, 7, 14, 40]. Note that these studies used the DII and not the E-DII. The present study had a DII range of −6.28 to +4.69 that was very similar to the E-DII range (−6.19 to +4.89). Dose–response analyses suggested E-DII threshold of ≈+2.5 to +3.0, which is greater than the one described previously and projects into a fourth quartile (E-DII: −0.55 to +4.89). The reason for this difference in thresholds may be related to different population characteristics (e.g., sample size, race, overall diet, confounding by unknown factors, possible correlation between E-DII and propensity for prostate cancer screening, or measurement error [e.g., dietary reporting bias according to social approval is more likely to occur in men, and there is evidence that it may not be monotonic]) [54]. For instance, in the French cohort, most participants were White, their diet was generally more proinflammatory (DII range: −5.0 to +5.3), and only 123 men developed prostate cancer [6]. The DII range in this study was much larger and skewed toward more anti-inflammatory diets (−6.28 to 4.69) than the range observed among Jamaican men (−3.14 to 2.77) [7]. In addition, the number of food parameters available for DII calculations may have contributed to the differences in risk estimates and thresholds.

Strengths of this study include a racially/ethnically diverse cohort, extended follow-up (up to 12 years), rigorous case ascertainment, and ample information on potential confounders. Sensitivity analyses after excluding participants diagnosed with prostate cancer during the first 3 years of follow-up indicated that reverse causation was unlikely to be a major issue although there was a chance of reverse causation beyond 3 years. A major advantage of the DII over other dietary indices is that it measures the inflammatory potential of the individual's diet based on reported intakes. Because the diet was assessed before prostate cancer diagnosis, differential recall according to outcome was not an issue. However, measurement errors still may have occurred and may have varied according to levels of potential confounders. Another study strength was its diversity; 35% of the study population was represented by racial and ethnic minorities (Asian, Black, Hispanic, and Filipino). The FFQ was modified for use among these men and included foods commonly eaten within those racial/ethnic groups; it also was translated into Spanish and Chinese. Thus, significant misclassification of the exposure based on unavailability of response options was unlikely.

This study also has several limitations. Information about diet was assessed only at baseline using a single FFQ. Thus, temporal changes in diet could not be evaluated. However, previous research

indicates that dietary patterns in adulthood are fairly stable over time [55–58]. Other prospective studies that used diet assessment only at baseline found that higher DII scores were associated with increased risks for chronic disease, including cancer incidence and mortality [31, 32, 59, 60]. In addition, there was no information on response sets, such as social approval and social desirability that have been shown to bias dietary self-report [54, 61, 62]. PSA testing was widespread within KP Northern California and was not done in a uniform manner as part of the CMHS (e.g., not done at baseline). Nonetheless, there may be some residual confounding if screening varied significantly by E-DII status. Another limitation was that sample size, and statistical power may have been limited for assessing the relationship between the E-DII and prostate cancer risk among substrata of race or by prostate cancer aggressiveness, and multiple comparisons were intentionally made. Because of the limitation of sample size, the observed nonlinear association may be because of chance. Blood biomarkers of inflammation (e.g., CRP) were not available for the entire cohort; therefore, it was not possible to correlate objective measures of inflammation with E-DII and prostate cancer risk. The construct validity of DII/E-DII in comparison to a variety of inflammation biomarkers has been established in 10 previous studies [18,21,22,63–67].

In summary, the results of this study suggest that the relationships between a proinflammatory diet and prostate cancer risk may be nonlinear. The risk appeared to rise above E-DII threshold of $\approx+2.5$ to $+3.0$ and appeared to be higher among men with high-risk prostate relative to those with prostate cancer of any stage and among Black and White men relative to other races. The relationship between dietary inflammatory potential and risk of advanced/aggressive disease merits further investigation, particularly among racial or ethnic minorities, before clinical and public health recommendations can be made.

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Authors' contributions: D.M.M. was responsible for conceptualization, formal analysis, writing the original draft, and reviewing and editing subsequent drafts. J.R.H. helped to conceptualize the study, provided access to the dietary inflammatory index, consulted on data analysis, participated in writing the original draft, and in reviewing and editing subsequent drafts. J.B.B. participated in writing the original draft and reviewing and editing subsequent drafts. J.W.H. provided high-level expertise for the statistical models and reviewed and edited all drafts of the article. J.Z. provided expertise for the statistical modeling and reviewed and edited the article. M.D.W. provided methodologic expertise, consulted on analyses, and reviewed and edited all drafts of the article. S.D.Y. provided methodologic expertise and reviewed and edited all drafts of the article. N.S. calculated the Dietary Inflammatory Index (DII) scores, reviewed results, and reviewed and edited all drafts of the article. S.J.J. provided methodologic expertise and reviewed all drafts of the article. B.C. helped to conceptualize the study, was the original principal investigator for the CMHS, consulted on data analyses, and reviewed and edited all drafts. S.K.V.D.E. helped to conceptualize the study, is the current principal investigator for the CMHS, consulted on data analyses, and reviewed and edited all drafts.

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Appendix A. Supplementary data

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