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# Are strict vegetarians protected against prostate cancer?<sup>1</sup>

Yessenia Tantamango-Bartley,<sup>2\*</sup> Synnove F Knutsen,<sup>2</sup> Raymond Knutsen,<sup>2</sup> Bjarne K Jacobsen,<sup>2,4</sup> Jing Fan,<sup>2</sup> W Lawrence Beeson,<sup>2</sup> Joan Sabate,<sup>2</sup> David Hadley,<sup>3</sup> Karen Jaceldo-Siegl,<sup>2</sup> Jason Penniecook,<sup>2</sup> Patti Herring,<sup>2</sup> Terry Butler,<sup>2</sup> Hanni Bennett,<sup>2</sup> and Gary Fraser<sup>2</sup>

<sup>2</sup>School of Public Health, Center for Nutrition, Healthy Lifestyle and Disease Prevention and <sup>3</sup>School of Medicine, Department of Urology, Loma Linda University, Loma Linda, CA; and <sup>4</sup>Department of Community Medicine, Universitetet i Tromsø, The Arctic University of Norway, Tromsø, Norway

## ABSTRACT

**Background:** According to the American Cancer Society, prostate cancer accounts for ~27% of all incident cancer cases among men and is the second most common (noncutaneous) cancer among men. The relation between diet and prostate cancer is still unclear. Because people do not consume individual foods but rather foods in combination, the assessment of dietary patterns may offer valuable information when determining associations between diet and prostate cancer risk.

**Objective:** This study aimed to examine the association between dietary patterns (nonvegetarian, lacto-ovo-vegetarian, pesco-vegetarian, vegan, and semi-vegetarian) and prostate cancer incidence among 26,346 male participants of the Adventist Health Study-2.

**Design:** In this prospective cohort study, cancer cases were identified by matching to cancer registries. Cox proportional hazards regression analysis was performed to estimate HRs by using age as the time variable.

**Results:** In total, 1079 incident prostate cancer cases were identified. Around 8% of the study population reported adherence to the vegan diet. Vegan diets showed a statistically significant protective association with prostate cancer risk (HR: 0.65; 95% CI: 0.49, 0.85). After stratifying by race, the statistically significant association with a vegan diet remained only for the whites (HR: 0.63; 95% CI: 0.46, 0.86), but the multivariate HR for black vegans showed a similar but nonsignificant point estimate (HR: 0.69; 95% CI: 0.41, 1.18).

**Conclusion:** Vegan diets may confer a lower risk of prostate cancer. This lower estimated risk is seen in both white and black vegan subjects, although in the latter, the CI is wider and includes the null. *Am J Clin Nutr* 2016;103:153–60.

**Keywords:** Adventist, cancer, diet, prostate, vegan

## INTRODUCTION

Prostate cancer (PCa) is the most common noncutaneous cancer in men. According to 2014 estimates from the American Cancer Society, PCa accounts for 27% (233,000 cases) of incident cancer cases among men in the United States (1).

Incidence of PCa varies greatly by geography, with the highest rates in economically developed countries (2). Possible explanations for this variation include environmental factors (3–6). Diet and nutrition have been estimated to account for ~30% of all cancers in developed countries and 20% in developing countries (7). Because of the need for long-term compliance after randomization to

specific diets, nutritional cancer epidemiology relies mainly on observation as opposed to intervention studies. One small randomized trial did, however, assess the effect of a lifestyle intervention on risk of progression in patients with early stage PCa who did not choose surgical treatment. The authors reported that an intervention consisting of a vegan diet and regular physical activity appeared to greatly reduce such progression (8).

To our knowledge, no prospective studies have compared specific vegetarian subtypes with nonvegetarian diets with regard to risk of PCa. Thus, the possible role of such dietary patterns to prevent incident PCa remains unclear. Dietary patterns contain information beyond that of single food items or nutrients because they include the total diet (9). Studying dietary patterns has some advantages because 1) individuals do not consume single nutrients, 2) the combinations and interactions of nutrients may affect their absorption and final metabolism, and 3) these eating patterns currently exist in real populations.

We investigate here the association between dietary patterns and the incidence of PCa in men from the Adventist Health Study-2 (AHS-2). This low-risk cohort provides a wide range of dietary habits in the context of overall good health. There is also diminished confounding by smoking and alcohol consumption, because these substances are avoided by most Adventists.

## METHODS

### Subjects

The study population consists of male participants in the AHS-2. These subjects were aged  $\geq 30$  y at enrollment and members of the Adventist Church who lived in the United States or Canada. Enrollment commenced in February 2002, and at completion (December 2007), more than 96,000 participants had completed the lengthy lifestyle questionnaire. Details of the scope of this study, how members were identified, and how their dietary and other lifestyle data were obtained have been described elsewhere (10).

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\*To whom correspondence should be addressed. E-mail: ytantamango@hotmail.com.

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For the 33,715 male participants in this prospective cohort study, the following exclusion criteria were applied: 1) subjects living in US states where cancer registry matching was unavailable (Maine and Wisconsin) or subjects living in Canada because their vital status is not yet established (2144 subjects); 2) prevalent cancers on baseline questionnaire (2753 subjects); 3) self-reported cases without consent to obtain medical records (8 subjects); 4) self-reported cases for whom medical records were not yet received and reviewed (26 subjects); 5) clearly invalid dietary responses, defined by identical nonzero responses across a whole page (144 subjects), or more than 69 missing questions in dietary data sometimes due to missing information on 2 facing pages (583 subjects); 6) age <25 y or missing data for age or sex (39 subjects); and 7) estimated calorie intake <500 kcal or >4500 kcal (830 subjects). Therefore, the analytic population becomes 27,188 male subjects.

### Dietary assessment

Dietary intake was assessed by a validated self-administered mailed food-frequency questionnaire (11). The food-frequency questionnaire contains a list of >200 food items, including fruits, vegetables, legumes, grains, oils, dairy products and eggs, meats (red meat, poultry, and fish), beverages, and commercially prepared products such as dietary supplements, dry cereals, meat substitutes, and soy milk.

Participants reported their average frequency of intake and serving size during the past year by using predefined frequency categories. Food variables that were of interest for this analysis included red meat, poultry, fish, eggs, and dairy products. The frequency categories for all red meat, poultry, and fish variables ranged from “never or rarely” to “2 times per day.” For dairy products, the range was from “never or rarely” to “6 times per day.” Three possible serving sizes were provided: standard,  $\leq 1/2$ , and  $> 1/2$  of the standard. This information was used to categorize subjects according to their vegetarian status. The meat variable was the composite of red meat [hamburger, beef (ground beef, processed beef, steak), bacon, ham, pork (sausage, chops, ribs, lunchmeat), and lamb] and poultry (chicken, turkey, processed chicken, or turkey). Fish included salmon, white fish, tuna, and other fish. The dairy variable was the composite of cheese, butter, milk, cottage cheese, cream cheese, evaporated milk, yogurt, and other dairy products. Thus, the following categories were defined related to vegetarian status: vegan, lacto-ovo-vegetarians, pesco-vegetarian, semi-vegetarian, and nonvegetarian. Vegans ate a total of red meat, poultry, fish <1 time/mo and eggs/dairy <1 time/mo; lacto-ovo-vegetarians ate a total of red meat, poultry, and fish <1 time/mo and eggs or dairy  $\geq 1$  time/mo; pesco-vegetarians consumed a total of red meat or poultry <1 time/mo but fish  $\geq 1$  time/mo and had no restriction on consumption of dairy products and/or eggs; semi-vegetarians ate a total of red meat or poultry  $\geq 1$  time/mo but all meats combined (including fish) <1 time/wk and eggs/dairy in any amount; and nonvegetarians ate a total of red meat and poultry  $\geq 1$  time/mo and all meats combined (including fish)  $\geq 1$  time/wk, as well as eggs or dairy in any amount. Energy-adjusted deattenuated correlation coefficients between meats (red meat, poultry, and fish) estimated from the food-frequency questionnaire and a reference measure (repeated 24-h recalls) were 0.86 (95% CI: 0.82, 0.90) and 0.85 (95% CI: 0.79, 0.89) for the white and black populations, respectively (11).

For the dairy variable, dairy protein showed energy-adjusted deattenuated correlations of 0.77 (95% CI: 0.73, 0.80) for whites and 0.58 (95% CI: 0.51, 0.64) for blacks. For dairy fat, correlations of 0.66 (95% CI: 0.61, 0.71) and 0.56 (95% CI: 0.49, 0.62) were observed for whites and blacks, respectively (12).

### Cancer ascertainment

Cancer cases were identified by computer-matching identifying information from AHS-2 study subjects to lists of cases in state cancer registries as previously described (10).

At this time, matches have been completed with all US states (with the exception of Maine and Wisconsin) and with Washington, DC.

In addition, biennial follow-up questionnaires were mailed to all participants that contained questions about new cancer diagnoses. If such self-reported cancers had not been found in the registry linkage, further follow-up was performed through a telephone interview to clarify whether it appeared to be a true cancer case. If so, medical records were requested and reviewed by the principal investigator.

New prostate cancer cases comprised only those where this malignancy was first diagnosed during the follow-up period, and subjects with previous noncutaneous cancers or cutaneous melanomas were excluded from analyses. The cancer site was identified by using the International Classification of Diseases, 10th Revision, Clinical Modification.

Advanced/high-grade prostate cancers were defined by using the SS2000 and Derived SS2000 staging codes provided by the Surveillance, Epidemiology, and End Results and Gleason score. Thus, advanced/high-grade cases constituted all cancers that were regional or metastatic (SS2000 or Derived SS2000 code  $\geq 2$ ) and/or cases with a Gleason score  $\geq 7$ . For a Gleason score of 7, only a primary grade of 4 and a secondary grade of 3 were considered advanced/high grade.

### Statistical analysis

The statistical package SAS version 9.3 (SAS Institute) was used for analyses in this study. Multiple imputation was used to fill in the small amount of missing data in the dietary variables used to define vegetarian status, this usually being guided by a random subsample of originally missing data that were subsequently filled in by telephone contact (13).

Sociodemographic characteristics of the population under study were analyzed without imputation of missing values and presented after standardization by age and race (14). Person-years of follow-up time were calculated as the time between the date of receiving the baseline questionnaire and 1) the date of a PCa diagnosis, 2) death, 3) relocation outside of the United States or Canada, or 4) the last date that complete cancer registry data (state of residence) were available and matched to AHS-2 data, whichever occurred first.

Univariate analysis was performed initially to evaluate the association between individual potential predictor factors and the PCa incidence. Next, multivariate Cox regression models were developed to estimate HRs and 95% CIs. Age was the time variable for the Cox proportional hazards models. All analyses were left censored. A basic model that included only the independent variables of interest and race was evaluated first. Other candidate covariates were selected based on review of the literature and added to this basic



model. These covariates included family history of PCa in a brother and/or father (yes/no), education (high school or less, some college, or at least college graduate), duration of vigorous activity (none, less than 60 min/wk, or at least 60 min/wk), BMI (in kg/m<sup>2</sup>; <25, 25–30, or >30), alcohol use within the past 2 y (yes/no), smoking status (ever/never), history of prostate hypertrophy (yes/no), personal history of diabetes mellitus (yes/no), total energy intake, and screening for PCa. For screening, a categorical variable was created to indicate those who reported that they had ever/never been screened with a prostate-specific antigen blood test. In

addition, a continuous time-lapse screening variable was created from the questionnaire time-lapse categories (0–2, 3–4, and ≥5 y ago) since the last prostate-specific antigen testing (scored respectively as 1, 3.5, and 7 y). The model contains the indicator variable and its product with the continuous variable, which nests the time lapse values within those subjects who screened.

Only covariates that changed the  $\beta$  coefficients for the exposure of interest by ≥10% were included in the final model. Thus, the final model included the basic model plus family history of PCa, education, screening for PCa, and calorie intake.

**TABLE 1**Sociodemographic characteristics of the male participants of the AHS-2 according to incident prostate cancer status<sup>1</sup>

Variable	Cases (%)			P value <sup>2</sup>	P value <sup>3</sup>
	Total (n = 1079)	Advanced (n = 237)	Noncases (n = 26,109, %)		
Age at baseline, y					
≤50	78 (7.23)	11 (4.64)	9411 (36.05)	<0.001	<0.0001
>50 to ≤59	213 (19.74)	28 (11.81)	5837 (22.36)		
>59 to ≤69	398 (36.89)	87 (36.71)	5238 (20.06)		
>69	390 (36.14)	111 (46.84)	5623 (21.54)		
Race					
White	784 (73.34)	180 (77.25)	20,038 (77.50)	0.001	0.93
Black	285 (26.66)	53 (22.75)	5818 (22.50)		
Education					
≤High school	193 (18.14)	51 (22.27)	5003 (19.37)	0.009	0.52
Some college	311 (29.23)	65 (28.38)	8449 (32.71)		
≥College graduate	560 (52.63)	113 (49.35)	12,375 (47.91)		
Family history of prostate cancer					
Yes	161 (14.92)	33 (13.92)	2406 (9.22)	<0.001	0.01
No	918 (85.08)	204 (86.08)	23,703 (90.78)		
BMI, kg/m <sup>2</sup>					
<25	349 (33.37)	65 (28.57)	9520 (37.42)	0.008	0.02
25–30	494 (47.23)	113 (49.13)	10,841 (42.61)		
>30	203 (19.41)	52 (22.61)	5082 (19.97)		
Vigorous exercise, min/wk					
None	186 (18.08)	45 (20.00)	4313 (17.24)	0.08	0.44
<60	317 (30.81)	70 (30.97)	8555 (34.19)		
≥60	526 (51.12)	110 (48.89)	12,155 (48.58)		
Smoking					
Ever	272 (25.81)	60 (25.97)	6662 (26.04)	0.87	0.98
Never	782 (74.19)	171 (74.03)	18,923 (73.96)		
Recent use of alcohol					
Yes (within past 2 y)	96 (8.94)	17 (7.17)	3027 (11.66)	0.006	0.03
No (or >past 2 y)	978 (91.06)	220 (92.83)	22,935 (88.34)		
Diabetes mellitus					
Yes	127 (11.80)	33 (13.98)	2430 (9.32)	0.006	0.02
No	949 (88.20)	203 (86.02)	23,637 (90.68)		
Prostate hypertrophy					
Yes	334 (31.04)	76 (32.07)	4348 (16.68)	<0.0001	<0.0001
No	742 (68.96)	161 (67.93)	21,719 (83.32)		
Screening					
Ever	867 (83.53)	186 (81.94)	14,974 (59.87)	<0.0001	<0.0001
Never	114 (16.47)	41 (18.06)	10,036 (40.13)		
Vegetarian dietary patterns					
Vegan	59 (5.47)	15 (6.33)	2081 (7.97)	0.003	0.60
Lacto-ovo-vegetarian	333 (30.86)	70 (29.54)	7766 (29.74)		
Pesco-vegetarian	121 (11.21)	28 (11.81)	2359 (9.04)		
Semi-vegetarian	63 (5.84)	13 (5.49)	1301 (4.98)		
Nonvegetarian	503 (46.62)	111 (46.84)	12,602 (48.27)		

<sup>1</sup>AHS-2, Adventist Health Study-2.<sup>2</sup>Test the hypothesis of no difference between total prostate cancer cases and noncases.<sup>3</sup>Test the hypothesis of no difference between advanced/high-grade prostate cancer cases and noncases.

Appropriate product terms were included to handle the nesting of the screening variable by age. The final multivariate HRs and CIs were calculated by combining results from 5 data sets with independent imputations of originally missing dietary data (15). Because dietary patterns have a strong correlation with BMI and because BMI may be an intermediate causal variable between diet and cancer risk, we also report final multivariate HRs from models with and without the inclusion of BMI, although the main results come from models without BMI included.

## RESULTS

During a mean follow-up of 7.8 y, we identified 1079 incident PCa cases. Among these, 237 advanced/high-grade cases were observed.

The baseline characteristics of the study population comparing incident cancers (total and advanced/high-grade cases) with non-cases are presented in **Table 1**. The median ages at PCa diagnosis were 66 and 68 y for the overall and advanced/high-grade cases, respectively. At baseline, incident cancer cases were older than noncases. Proportionally more blacks (4.67%) had a PCa diagnosis than whites (3.77%). Men with PCa were slightly more educated and had a higher BMI but performed vigorous physical activity with a similar frequency to those who did not develop the disease. Recent use of alcohol consumption was less frequently reported among the PCa participants, but there was no difference observed for history of smoking between cases and noncases. Prevalence of diabetes mellitus and prostatic hypertrophy was higher among the PCa cases, and PCa patients were more likely to have ever been screened for PCa. A lower proportion of vegans

**TABLE 2**  
Baseline characteristics of the male participants of the AHS-2 by dietary patterns<sup>1</sup>

Variable	Vegetarian, n (%)				Nonvegetarian, n (%)	P value
	Vegan	Lacto-ovo-vegetarian	Pesco-vegetarian	Semi-vegetarian		
Age at baseline, y						
≤50, n = 9489	704 (32.90)	2560 (31.61)	792 (31.94)	454 (33.28)	4979 (37.99)	<0.001
>50 to ≤59, n = 6050	495 (23.13)	1782 (22.00)	489 (19.72)	280 (20.53)	3004 (22.92)	
>59 to ≤69, n = 5636	441 (20.61)	1641 (20.26)	536 (21.61)	298 (21.85)	2720 (20.76)	
>69, n = 6013	500 (23.36)	2116 (26.13)	663 (26.73)	332 (24.34)	2402 (18.33)	
Race						
White, n = 20,995	1755 (82.39)	7134 (88.08)	1674 (67.50)	1184 (86.80)	9238 (70.49)	<0.001
Black, n = 6193	375 (17.61)	965 (11.92)	806 (32.50)	180 (13.20)	3867 (29.51)	
Education						
≤High school, n = 5276	377 (17.62)	1059 (13.08)	468 (18.87)	269 (19.72)	3103 (23.68)	<0.001
Some college, n = 8874	680 (31.78)	2124 (26.23)	793 (31.98)	424 (31.09)	4853 (37.03)	
≥College graduate, n = 13,038	1083 (50.61)	4916 (60.70)	1219 (49.15)	671 (49.19)	5149 (39.29)	
Family history of PCa						0.001
Yes, n = 2567	194 (9.07)	854 (10.54)	232 (9.35)	133 (9.75)	1154 (8.81)	
No, n = 24,621	1946 (90.93)	7245 (89.46)	2248 (90.65)	1231 (90.25)	11,951 (91.19)	
BMI, kg/m <sup>2</sup>						
<25, n = 10,115	1417 (66.21)	3701 (45.70)	1065 (42.94)	521 (38.20)	3411 (26.03)	<0.001
25–30, n = 11,654	580 (27.10)	3288 (40.60)	1094 (44.11)	607 (44.50)	6085 (46.43)	
>30, n = 5419	143 (6.68)	1110 (13.71)	321 (12.94)	236 (17.30)	3609 (27.54)	
Exercise, min/wk						
None, n = 4699	291 (13.60)	1223 (15.05)	380 (15.33)	234 (17.13)	2571 (19.66)	<0.001
<60, n = 9259	671 (31.36)	2780 (34.22)	788 (31.79)	488 (35.72)	4532 (34.65)	
≥60, n = 13,230	1178 (55.05)	4121 (50.73)	1311 (52.88)	644 (47.14)	5976 (45.69)	
Recent use of alcohol						<0.001
Yes, n = 13,243	47 (2.21)	258 (3.21)	173 (7.03)	118 (8.70)	2524 (19.41)	
No, n = 13,945	2082 (97.79)	7789 (96.79)	2289 (92.97)	1238 (91.30)	10,480 (80.59)	
Smoking						
Ever, n = 7222	459 (21.45)	1324 (16.35)	559 (22.54)	344 (25.22)	4536 (34.61)	<0.001
Never, n = 19,966	1681 (78.55)	6775 (83.65)	1921 (77.46)	1020 (74.78)	8569 (65.39)	
Diabetes mellitus						<0.001
Yes, n = 2565	100 (4.67)	507 (6.26)	193 (7.78)	132 (9.68)	1633 (12.46)	
No, n = 24,623	2040 (95.33)	7592 (93.74)	2287 (92.22)	1232 (90.32)	11,472 (87.54)	
Prostatic hypertrophy						0.005
Yes, n = 1635	97 (4.53)	502 (6.20)	180 (7.26)	86 (6.30)	770 (5.88)	
No, n = 25,553	2043 (95.47)	7597 (93.80)	2300 (92.74)	1278 (93.70)	12,335 (94.12)	
Screening						<0.001
Ever, n = 15,841	1113 (54.67)	4930 (62.83)	1578 (66.69)	809 (61.99)	7404 (59.29)	
Never, n = 10,207	923 (45.33)	2916 (37.17)	788 (33.31)	496 (38.01)	5084 (40.71)	

<sup>1</sup>P value tests the hypothesis of no difference between dietary patterns for the baseline characteristics being examined. AHS-2, Adventist Health Study-2; PCa, prostate cancer.



was observed among the cancer group. As shown, similar socio-demographic information was observed for advanced/high-grade disease, with broadly similar results also compared with noncases, although a difference was the lack of statistically significant differences between noncases and advanced/high-grade cases for race, education, and vegetarian dietary patterns (no covariate adjustments).

The sociodemographic characteristics of the participants comparing nonvegetarian with vegetarian subjects are shown in **Table 2**. A higher proportion of nonvegetarians was observed among the younger population, whereas older men were more likely to be lacto-ovo-vegetarians and pesco-vegetarians. Compared with whites, blacks were less likely to be vegetarian. Blacks who were vegetarian were more likely to be pesco-vegetarians. Non-vegetarians were less educated, more overweight/obese, and less likely to perform regular vigorous physical activity for more than 60 min/wk than vegetarians. Lacto-ovo-vegetarians had the highest amount of education and vegans had by far the lowest proportion of overweight and obese participants. Compared with vegetarian groups, nonvegetarians were more likely to have consumed alcohol within the past 2 y or ever smoked cigarettes. They were also more likely to have a history of diabetes mellitus, and vegans were the least likely to have this diagnosis. Vegans were also statistically significant less likely to have ever been screened for PCa and have a history of prostatic hypertrophy than nonvegetarians (16).

Proportional hazards analyses associating diet with risk of PCa are shown in **Table 3**. A strong, inverse association between the vegan diet and PCa risk was observed in the age-adjusted analysis compared with the nonvegetarian group. This association remained significant after controlling by race, family history of PCa, education, screening, and calorie intake (HR: 0.65; 95% CI: 0.49, 0.85). Analyses restricted to advanced/high-grade cancer cases did not show a statistically significant association with any vegetarian dietary pattern ( $P > 0.1$ ). However, the point estimate for the association with vegan diet (HR: 0.70; 95% CI: 0.41, 1.21) was close to that for overall PCa cases (HR: 0.65). Adjusting for BMI in these analyses changed the vegan HR toward the null, perhaps indicating that BMI partially mediates a dietary effect.

When we stratified the analyses by race (**Table 4**), the interaction terms between vegan diet and race were not significant ( $P = 0.76$ ). The statistically significant protective association between the vegan diet and total PCa risk remained only for whites, although the point estimate for this association among blacks was similar in magnitude (HR: 0.69; 95% CI: 0.41, 1.18) but not statistically significant. As before, the inclusion of BMI in the multivariate model did not greatly modify the observed effect of the different dietary patterns on PCa risk when examined separately among the 2 racial groups. Again there was no statistically significant association between dietary pattern and the risk of advanced/high-grade cases of PCa after stratification by race (data not shown), although numbers were small especially among blacks.

We performed 2 sensitivity analyses to evaluate the possible confounding effect of less cancer screening among vegans. First, the screening variable is associated with risk of PCa, which suggests that it possesses some validity. Yet when leaving it out of the model, the HR for the vegan effect did not change (HR: 0.65; 95% CI: 0.49, 0.85). Second, we performed analyses stratified by screening status. The point estimate for vegans was weaker in those who did not screen within the past 2 y or never screened (HR: 0.76; 95% CI: 0.49, 1.17) than in those who screened within the past 2 y (HR: 0.65; 95% CI: 0.46, 0.92), but numbers of vegan cases were small in the nonscreening/less frequent screening group ( $n = 24$ ) with wide CIs, which easily includes the result among the more frequent screeners.

## DISCUSSION

Our findings demonstrate a protective association of the vegan diet with risk of PCa compared with subjects subscribing to a nonvegetarian diet. This association is clearly evident among whites, and the estimate among blacks is very similar but not statistically significant. The estimate for the association between a vegan diet and advanced/high-grade PCa is also similar to that for all cases, although again with wider CIs and not close to statistical significance. BMI does not seem to substantially modify these associations, despite being strongly associated with dietary pattern.

**TABLE 3**

Age-adjusted and multivariate-adjusted HRs of the association between vegetarian dietary patterns and prostate cancer incidence

Variable	Vegan	Lacto-vegetarian	Pesco-vegetarian	Semi-vegetarian	Nonvegetarian
Overall prostate cancer					
Events, <i>n</i>	59	333	121	63	503
Person-years	15,794.80	58,676.30	17,629.70	9691.50	92,569.30
IR <sup>1</sup> × 100,000	373.54	567.52	686.34	650.05	543.38
HR <sup>2</sup> (95% CI)	0.64 (0.48, 0.83)	0.94 (0.81, 1.08)	1.12 (0.92, 1.37)	1.11 (0.85, 1.46)	1.00
HR <sup>3</sup> (95% CI)	0.65 (0.49, 0.85)	0.96 (0.83, 1.10)	1.06 (0.87, 1.30)	1.18 (0.91, 1.53)	1.00
HR <sup>4</sup> (95% CI)	0.66 (0.50, 0.87)	0.96 (0.83, 1.12)	1.07 (0.88, 1.31)	1.18 (0.91, 1.54)	1.00
Advanced prostate cancer					
Events, <i>n</i>	15	70	28	13	111
Person-years	15,657.10	57,825.00	17,545.70	9441.00	90,603.80
IR × 100,000	95.80	121.05	159.58	137.70	122.51
HR <sup>2</sup> (95% CI)	0.70 (0.41, 1.20)	0.84 (0.62, 1.13)	1.09 (0.72, 1.66)	1.00 (0.56, 1.78)	1.00
HR <sup>3</sup> (95% CI)	0.70 (0.41, 1.21)	0.86 (0.63, 1.17)	1.05 (0.69, 1.59)	1.07 (0.60, 1.90)	1.00
HR <sup>4</sup> (95% CI)	0.78 (0.45, 1.35)	0.91 (0.66, 1.24)	1.10 (0.72, 1.68)	1.09 (0.61, 1.95)	1.00

<sup>1</sup>IR, incidence rate.

<sup>2</sup>Age-adjusted model.

<sup>3</sup>Multivariate model 1: includes race, family history of prostate cancer, education, screening for prostate cancer, and kcal.

<sup>4</sup>Multivariate model 2: includes model 1 plus BMI.

**TABLE 4**

Multivariate-adjusted HRs of the association between vegetarian status and specific dietary patterns and prostate cancer incidence stratified by race

Dietary pattern	Black			White		
	Events, <i>n</i>	HR <sup>1</sup> (95% CI)	HR <sup>2</sup> (95% CI)	Events, <i>n</i>	HR <sup>1</sup> (95% CI)	HR <sup>2</sup> (95% CI)
Nonvegetarian	174			329		
Vegan	15	0.69 (0.41, 1.18)	0.67 (0.39, 1.15)	44	0.63 (0.46, 0.86)	0.65 (0.47, 0.90)
Lacto-ovo-vegetarian	41	0.81 (0.57, 1.14)	0.80 (0.56, 1.13)	292	0.98 (0.83, 1.15)	1.00 (0.85, 1.18)
Pesco-vegetarian	46	1.18 (0.85, 1.63)	1.16 (0.84, 1.62)	75	1.00 (0.78, 1.29)	1.03 (0.80, 1.32)
Semi-vegetarian	14	1.55 (0.90, 2.69)	1.54 (0.89, 2.67)	49	1.10 (0.81, 1.48)	1.11 (0.82, 1.50)

<sup>1</sup>Multivariate model 1: includes family history of prostate cancer, education, screening for prostate cancer, and kcal.<sup>2</sup>Multivariate model 2: includes model 1 plus BMI.

The relation between different dietary patterns and PCa risk in other studies has not been clear. A small Iranian case-control study found that subjects who scored higher compared with those who scored lower on a “Western dietary pattern” scale had a substantial elevated risk of PCa, and those who scored higher on a “healthy” diet scale had lower risk (17). On the other hand, prospective studies in the United States have defined “prudent,” “Western,” “Southern,” “red meat–starch,” and “vegetable–fruit” patterns and did not find clear associations (18, 19).

Associations between particular vegetarian dietary patterns and PCa risk have rarely been studied previously. A protective association with a vegetarian diet has been reported for moderate compared with low/none (OR: 0.67; 95% CI: 0.47, 0.94) by one case-control study from Taiwan (20). To our knowledge, there is no information available about the effect of a vegan diet on the risk of developing PCa. However, a randomized, prospective clinical trial of men with clinically localized PCa who had selected “watchful waiting” as primary therapy tested a lifestyle change that included a low-fat, soy-supplemented vegan diet plus an exercise program. This study showed a 70% reduction of progression of PCa to a more advanced stage compared with the nonintervention control group ( $P < 0.001$ ) after 1 y of follow-up (8).

A vegan diet is not defined by what it incorporates but rather by what is omitted (21). Compared with nonvegetarians, in this population, vegans were found to consume less fat, protein, zinc, calcium, vitamin D, vitamin E, sodium, and phosphorus but more carbohydrate, fiber, polyunsaturated compared with saturated fat, vitamin C, vitamin B-6, folate, vitamin B-12,  $\beta$ -carotene, potassium, magnesium, and plant-derived iron concentrations (22). Although vegans, in general, have been reported to have more diverse nutrient sources and to frequently use supplements (21), in our population, with the exception of vitamin B-12, they supplemented less frequently than others (22). Lower intakes of certain nutrients may affect cancer risk. For instance, less animal protein may reduce serum insulin-like growth factor 1 (23), which is a potent growth factor for normal prostatic epithelium, as well as for prostate adenocarcinoma cell lines. Insulin-like growth factor 1 may inhibit apoptosis in many normal (24) and neoplastic cell lines, and apoptosis of genetically damaged cells is crucial to cancer prevention (23). Vegans in the United Kingdom have lower concentrations of serum insulin-like growth factor 1, and higher concentrations have been statistically significant and strongly associated with risk of PCa in several epidemiologic studies (25–27).

Vegans are also characterized by their avoidance of dairy products. There is inconsistent evidence of the association between

PCa risk and dairy products intake (24, 28–32) and/or calcium (24, 29, 33–35). Potential causal mechanisms include 1) the high saturated fat content of dairy products (21), which has been consistently associated with insulin resistance (36), which in turn has been associated with an increased risk of PCa (37); 2) the high animal protein content of dairy products (38); and 3) the suppression by calcium of calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>), the metabolically active form of vitamin D. Vitamin D may inhibit cancer formation by inducing cell differentiation, apoptosis, and cellular arrest (21), although published literature provides little evidence to support a major role of vitamin D in preventing PCa or its progression (39, 40).

Epidemiologic, histopathologic, and molecular studies suggest that chronic inflammation may play an important role in the development and progression of PCa (41–43). Chronic inflammation is associated with oxidative stress and free radical production, which can damage genomic DNA and enhance the development of prostate carcinogenesis (44). Vegans consume large amounts of foods rich in antioxidants (22), which is associated with reduced inflammation (44). A vegan diet has also been associated with lower concentrations of serum C-reactive protein, a marker of inflammation (45, 46).

Soy is an important source of complete protein in the vegan diet, and in the Adventist population, vegans consume more soy than those adopting other dietary patterns (47). Consumption of soy foods has been associated with a reduced risk of PCa in different epidemiologic studies (48–51). Biological mechanisms by which soy may reduce the risk of PCa include 1) decreased cancer cell growth through inhibition of protein tyrosine kinase–mediated signaling mechanisms; 2) inhibition of topoisomerases I and II and protein histidine kinase, which have antiproliferative or proapoptotic effects; 3) antioxidant effects through inhibition of the expression of stress-response related genes; 4) inhibition of nuclear transcription factor  $\kappa$ B and AKt signaling pathways, which are important for cell survival; 5) inhibition of angiogenesis; 6) downregulation of transforming growth factor  $\beta$ ; and 7) inhibition of epidermal growth factor (52).

When stratifying by race, the point estimate for a vegan diet among blacks was very similar to that observed among whites, although no longer statistically significant. In addition, vegans had lower estimated HRs for advanced/high-grade PCa cases, but this also did not reach statistical significance. Due to the relatively small number of black vegans and vegans with a diagnosis of advanced/high-grade disease in this population, statistical power is reduced and CIs are wide, but there is a suggestion of consistency in these results.



Strengths of this study are its prospective design and the validation of new PCa through cancer registries or by review of medical records. In addition, the wide variety of dietary habits and the very low prevalence of alcohol consumption and cigarette smoking increase statistical power and reduce possible confounding by these factors.

Potential limitations include unavoidable inaccuracies in the assessment of food consumption, although these are probably less influential when assigning a dietary pattern than when calculating intake of a particular food or nutrient. Participants may have overestimated some foods generally considered beneficial, due to social desirability. However, such misclassification should be nondifferential, usually biasing the results toward the null. Furthermore, our published data (11) comparing the questionnaire with six 24-h dietary recalls suggest good validity for the foods used to determine the vegetarian categories.

The lower screening rate among vegans (16) and that screening is associated with higher risk of apparent PCa (probably a diagnostic bias) raises the possibility of residual confounding. However, the significant association seen in the sensitivity analysis among recent screeners is an important result. The validity of reporting should be relatively good for such recent screening. Moreover, given that such individuals had screened within that time frame, the opportunity for residual confounding is quite limited and seems unlikely to constitute an explanation for the observed association between vegans and risk of PCa. A limitation is that screening habits during follow-up after baseline were not assessed. Residual confounding by other variables measured with error, including those defining the vegan diet, also cannot be excluded.

In conclusion, these analyses provide evidence that subjects adhering to a vegan diet experience a lower incidence of PCa than those preferring a nonvegetarian diet. Vegan diets differ from other vegetarian and nonvegetarian diets by the absence of dairy and eggs, as well as greater intake of most fruit, vegetables, nuts, and legumes. This raises the possibility of a causal connection between some of these factors or their combination, given the existence of potential mechanisms, the appearance of consistency in results among subgroups, and the lack of obvious residual confounding.

The authors' responsibilities were as follows—YT-B: analyzed data, wrote the paper, and had primary responsibility for the final content of the manuscript; SFK, BKJ, JF, JS, and DH: provided input to the content of the manuscript, study design, data analysis development, or statistical analysis; YT-B, SFK, GF: designed research, assisted with data analysis, or assisted with the development of overall research plan; PH and TB: contributed to the overall design of the Adventist Health Study-2; RK and KJ-S: provided assistance with the definition of vegetarian variables and other food/nutrient variables or specific variables; JF: constructed databases necessary for the research; WLB: contributed to the record linkage between Adventist Health Study-2 and the State Cancer Registries; JP: assisted with literature review; HB: was responsible for the administrative affairs between the Adventist Health Study-2 and the state cancer registries; and GF: helped develop the manuscript and its final content. Conclusions from this study express the results from our findings and not an official position of Loma Linda University or our funders. None of the authors declared a conflict of interest related to this study.

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