

Vegetables, Fruits, Legumes and Prostate Cancer: A Multiethnic Case-Control Study¹

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Abstract

The evidence for a protective effect of vegetables, fruits, and legumes against prostate cancer is weak and inconsistent. We examined the relationship of these food groups and their constituent foods to prostate cancer risk in a multicenter case-control study of African-American, white, Japanese, and Chinese men. Cases ($n = 1619$) with histologically confirmed prostate cancer were identified through the population-based tumor registries of Hawaii, San Francisco, and Los Angeles in the United States and British Columbia and Ontario in Canada. Controls ($n = 1618$) were frequency-matched to cases on ethnicity, age, and region of residence of the case, in a ratio of approximately 1:1. Dietary and other information was collected by in-person home interview; a blood sample was obtained from control subjects for prostate-specific antigen determination. Odds ratios (OR) were estimated using logistic regression, adjusting for age, geographic location, education, calories, and when indicated, ethnicity. Intake of legumes (whether total legumes, soyfoods specifically, or other legumes) was inversely related to prostate cancer (OR for highest relative to lowest quintile for total legumes = 0.62; P for trend = 0.0002); results were similar when restricted to prostate-specific antigen-normal controls or to advanced cases. Intakes of yellow-orange and cruciferous vegetables were also inversely related to prostate cancer, especially for advanced cases, among whom the highest quintile OR for yellow-orange vegetables = 0.67 (P for trend = 0.01) and the highest quintile OR for cruciferous vegetables = 0.61 (P for trend = 0.006). Intake of tomatoes and of fruits

was not related to risk. Findings were generally consistent across ethnic groups. These results suggest that legumes (not limited to soy products) and certain categories of vegetables may protect against prostate cancer.

Introduction

The incidence of prostate cancer exceeds that of all other cancers among men in Canada and among white and African-American men in the United States (1). Although a role of diet in prostate cancer is suspected, the nature of this relationship is unclear (2). Many studies have shown positive associations between dietary fat, especially saturated fat, and prostate cancer risk (3), and some studies have reported inverse associations with higher intake of vegetables; the findings with regard to fruit intake are more equivocal (2). Scattered reports have associated several other foods and nutrients with prostate cancer (4).

In an earlier report of a multicenter case-control study that included African-Americans, whites, and Asians (Japanese and Chinese), representing populations at high, intermediate, and low risk of prostate cancer, respectively, we found an increased risk of the disease in men who consumed higher intakes of saturated fat, after adjustment for energy and other potential confounders (5). In the present investigation, we examined particular foods and food groups that potentially could reduce the risk of prostate cancer. We elected to base this analysis on foods (vegetables, fruits, and legumes), rather than on particular food constituents, because of the large number and variety of compounds in these foods with potential cancer-promoting or -inhibiting properties. In addition to the individual food items, we examined selected food groups. For vegetables, these included total, dark green, yellow-orange, and cruciferous; for fruits, total, and citrus; and for legumes, total, soyfoods, and "other." A particular focus of the analysis was on the degree of consistency in findings among the different ethnic groups.

Materials and Methods

Selection of Cases and Controls. Cases were men up to 84 years of age with histologically confirmed prostate cancer, identified through the population-based tumor registries of Hawaii, San Francisco, and Los Angeles in the United States and British Columbia and Ontario in Canada. In Hawaii, cases were restricted to the island of Oahu, and in British Columbia and Ontario, cases were restricted to the greater metropolitan areas of Vancouver and Toronto, respectively. For African-Americans and whites, the cases were diagnosed between 1989 and 1991, and for the Chinese and Japanese, between 1987 and 1991. Other eligibility requirements included residence in the geographic area covered by one of the registries and having at least three of the four grandparents of the same ethnicity (either white, African-American, Japanese, or Chinese). African-

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Americans were selected from Los Angeles and San Francisco only. Whites were selected from the three United States centers, and Asian-Americans were selected from all five areas. For cases who had died, a next-of-kin was eligible to respond as a surrogate, provided the person had lived with the subject and/or knew his usual diet and physical activity patterns in the year prior to diagnosis; only 9% of the interviews were done with surrogates. The overall response rate for the cases was 70%, ranging from 79% among the Japanese to 64% among African-Americans.

Controls were frequency-matched to cases on ethnicity, age at the dietary reference period (5-year intervals), and region of residence of the case, in a ratio of approximately 1:1. In Hawaii, controls were identified through the Health Surveillance Program of the Department of Health, which each year randomly selects ~2% of state households for a health interview survey. In Los Angeles and San Francisco, controls were identified through random-digit dialing, with area codes and prefixes weighted in proportion to their respective distributions among all registered cancer patients in the particular region. Additional controls 65 years and older were obtained by random selection from computerized lists of the Health Care Financing Administration. In British Columbia, controls were randomly selected from rosters of the provincial Medical Services Plan, and in Toronto, controls were selected from an age-stratified random sample of the geographic area defined for the cases, based on provincial property assessment lists that cover the entire population. The overall response rate for the controls was 58%, ranging from 71% among the Japanese to 45% among African-Americans.

Data Collection. Subjects were interviewed in their homes by trained interviewers using the language or dialect of their choice. The questionnaire was translated into Chinese; no other language translation was needed. Questionnaire content included demographics, diet, body size, physical activity, and medical history. Information on migration was obtained for the Asian-Americans. The reference period for the dietary and nondietary questions was the year before diagnosis or symptoms for the cases and the year before interview for the controls.

The diet history included 147 food items or food groups, encompassing the following categories: soups, poultry and fish, processed meats, other meats, eggs, mixed dishes, ethnic foods, potatoes and rice, pasta, legumes, vegetables, fruits, juices, breads, cheese and milk, desserts and snacks, and beverages. Food items were selected to include the most frequently consumed foods in each ethnic group and to capture at least 85% of the intake of the major nutrients of interest for all participants. The men reported both frequency and portion size for each food item consumed at least 12 times per year. Identification of serving size was facilitated by the use of colored photographs showing the items in three portion sizes based on distributions observed in a series of food records collected earlier in these same populations. Information was also collected on frequency and dosages of vitamin supplement use (β -carotene, calcium, selenium, and vitamins A, C, D, and E), but these data are not included in the present analysis, which is focused on foods. A total of 36 cases and 27 controls were excluded from the analysis because of missing data on diet or education or because the interviewer rated the interview as unreliable.

Estimates of caloric and saturated fat intake (used as adjustment variables in the analyses) were derived from the questionnaire data, using a food composition table specially created for this project. The latter was based on the United

States Department of Agriculture (6), supplemented with data from a variety of other sources (7–9), including local laboratory analyses (10). Estimates of fat intake accounted for the use of fats and oils in cooking, as well as trimming of fat from meats and removal of skin from poultry. Determination of vegetable intakes included their contributions to mixed dishes. For example, consumption of cooked tomatoes for each subject was based on the estimated amounts of tomato in pizza, spaghetti sauce, stews, stir-fries, and others.

Blood samples were collected on the controls in all areas except Toronto (76% of eligible men responded) to identify (based on PSA³ level) men with potentially malignant occult prostate disease. The study protocol was approved by the Institutional Review Board at each center, and all participants provided written informed consent.

Statistical Analyses. Cases were classified according to stage and grade. Advanced cases were defined as men whose disease had extended beyond the capsule of the gland or whose disease was localized but the tumor was poorly or only moderately differentiated (11). Controls were classified according to PSA level in age-specific groupings, based on the 95th percentiles of PSA concentrations in a community sample of white men who were clinically free of prostate cancer (12). Men were considered PSA-normal if the level was ≤ 4.4 ng/ml (age 49 or younger), 6.2 (ages 50–59), 8.0 (ages 60–69), and 11.6 (ages 70 or older). We used the same cutpoints for all groups, because ethnic-specific cutpoints have not yet been established and are still controversial.

Food intakes were categorized into quantiles based on daily intakes (g) in the combined group of all controls. Quintiles were used for analyses that included all ethnicities; tertiles were used for ethnic-specific analyses. Common cutpoints were used for ethnic-specific models and other subgroup analyses. Indicator variables were created to represent quantile membership. ORs and 95% CIs were estimated using logistic regression (13), adjusting for age, geographic region, education, and caloric intake. Because the distribution for calories was highly skewed, log transformation was used for this adjustment variable. Ethnicity was adjusted for when appropriate. Trend was tested by entering a variable assigned the median for the food quantile. Regressions were performed using SAS software (14). All *P*s are two-sided. Analyses were conducted first using all cases and all matched controls. Additional analyses included men with advanced tumors only and controls with normal PSA levels only. A fuller description of the methods for this study can be found in an earlier report (5).

Results

Table 1 shows some characteristics of the subjects for the reference period 1 year prior to diagnosis (cases) or interview (controls). Cases and controls were well matched on age in all ethnic groups, and mean educational level was comparable within the groups. Cases and controls were similar in terms of body mass index within ethnic group, although there were noticeable differences across groups on this variable. In all groups, cases consumed more total calories and more total and saturated fat than controls (Table 1), although this difference disappeared in the African-Americans and whites after adjustment for calories (data not shown). Cases also consumed more fruits and vegetables than controls in all groups, except the

³ The abbreviations used are: PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval.

Table 1 Mean characteristics of study subjects by ethnicity and disease status

Ethnicity/Disease status	n	Age (yr)	Education (yr)	BMI ^a (kg/m ²)	Total calories (kcal/day)	Fat (g/day)	Saturated fat (g/day)	Fruits and vegetables (g/day)	Legumes (g/day)
African-American									
Case	505	69.3	10.5	26.3	2456	102.7	33.2	495.2	46.2
Control	519	69.2	10.9	26.7	2386	98.8	31.7	465.9	52.6
White									
Case	510	70.6	14.1	25.7	2268	91.7	29.7	491.3	39.3
Control	501	69.8	14.5	25.6	2177	87.6	28.6	470.4	40.9
Japanese									
Case	325	70.9	11.8	24.5	2187	78.3	22.8	478.1	71.5
Control	329	70.7	12.2	24.2	2057	71.4	20.0	475.2	82.9
Chinese									
Case	279	72.3	11.9	23.5	2162	73.0	21.4	432.5	43.6
Control	269	71.2	11.6	23.2	2042	63.2	18.3	434.2	48.0

^a BMI, body mass index.

Table 2 Pearson product-moment correlation coefficients between pairs of selected food groups^{a,b}

	1	2	3	4	5	6	7	8	9
1									
All vegetables	1.00	0.61	0.59	0.59	0.24	0.22	0.29	0.32	0.36
2									
Dark green vegetables	0.58	1.00	0.35	0.86	0.14	0.13	0.24	0.07	0.06
3									
Yellow-orange vegetables	0.52	0.29	1.00	0.34	0.25	0.21	0.25	0.26	0.25
4									
Cruciferous vegetables	0.56	0.85	0.29	1.00	0.13	0.12	0.25	0.03	0.04
5									
All fruits	0.14	0.08	0.18	0.08	1.00	0.77	0.15	0.09	0.13
6									
Citrus fruits	0.13	0.09	0.15	0.07	0.76	1.00	0.10	0.10	0.15
7									
All legumes	0.16	0.17	0.15	0.19	0.07	0.03	1.00	0.68	0.20
8									
Legumes excluding soyfoods	0.17	-0.02	0.16	-0.06	-0.01	0.03	0.63	1.00	0.41
9									
Saturated fat	-0.06	-0.23	-0.06	-0.27	-0.15	-0.05	-0.12	0.21	1.00

^a Food intakes and saturated fat (g/day) were log transformed.

^b Values to the right of the diagonal are unadjusted correlation coefficients; values to the left of the diagonal are partial correlation coefficients, adjusted for total energy intake.

Chinese; after adjustment for calories, African-American and white cases still had higher intakes than the corresponding controls. In contrast, cases in all groups had a lower mean intake of legumes than the corresponding controls, and these differences persisted after adjustment for calories.

Table 2 shows Pearson product-moment correlation coefficients among the various categories of vegetables and fruits examined in the analysis and between these food groupings and saturated fat, with and without adjustment for total energy intake. (Spearman's rank correlations gave almost identical values.) Because of the large number of foods within these categories, correlation coefficients for individual foods are not shown in the table. Correlations between the major categories (vegetables, fruits, and legumes) are low in all instances. Within vegetables, the intake of dark green vegetables is moderately correlated with yellow-orange vegetables and is highly correlated with cruciferous vegetables, which is not unexpected because there is overlap in several of the foods in the dark green and cruciferous groups (see "Appendix"). In the unadjusted analysis, saturated fat intake is moderately correlated with the intake of all vegetables ($r = 0.36$) and with legumes excluding soyfoods ($r = 0.41$); however, these correlations disappear after

adjustment for total energy intake ($r = -0.06$ and 0.21 , respectively).

Table 3 shows the results of the logistic regression analyses for vegetables and fruits in all ethnic groups combined, adjusted for ethnicity, age, education, geographic location, and total caloric intake. Because we had found a significant association of prostate cancer risk with the intake of saturated fat in our earlier report (5), we repeated the analysis with saturated fat in the model; however, the results were unchanged. Similarly, adjustment for monounsaturated and polyunsaturated fatty acids had no material effect on the findings. The table shows the results for each of the vegetable and fruit groups examined but only for selected individual vegetables and fruits that either showed a significant finding (corn and carrots) or were items of particular prior interest (tomatoes and papaya). A list of the items included in the various groupings of vegetables and fruits is included in the "Appendix."

The initial analysis included all cases and all controls in the study. Two of the three vegetable groupings (yellow-orange and cruciferous) show an inverse relationship to prostate cancer risk, and the trend for the cruciferous vegetables is statistically significant ($P = 0.02$). All vegetables combined also shows a

Table 3 Prostate cancer risk according to quintiles of intake of vegetables and fruits

Food item or group	Quintile					P for trend
	1 (low)	2	3	4	5 (high)	
Dark green vegetables						
Quintile range (g/day)	≤7.8	7.9–17.9	18.0–32.8	32.9–61.0	>61.0	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	1.18 (0.95–1.48)	1.02 (0.81–1.29)	1.09 (0.87–1.37)	0.98 (0.77–1.25)	0.41
All cases/normal controls ^c	1.00	1.14 (0.87–1.49)	1.09 (0.83–1.44)	1.22 (0.92–1.62)	1.12 (0.83–1.51)	0.63
Advanced cases/all controls ^d	1.00	1.17 (0.85–1.60)	0.74 (0.52–1.04)	0.94 (0.66–1.29)	0.88 (0.62–1.24)	0.35
Yellow-orange vegetables						
Quintile range (g/day)	≤6.3	6.4–13.2	13.3–22.4	22.5–38.5	>38.5	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.86 (0.69–1.07)	0.74 (0.59–0.93)	0.72 (0.57–0.90)	0.79 (0.63–1.00)	0.14
All cases/normal controls ^c	1.00	0.77 (0.58–1.01)	0.74 (0.56–0.98)	0.68 (0.51–0.90)	0.73 (0.55–0.98)	0.12
Advanced cases/all controls ^d	1.00	0.98 (0.72–1.33)	0.77 (0.55–1.06)	0.62 (0.44–0.87)	0.67 (0.48–0.94)	0.01
Cruciferous vegetables						
Quintile range (g/day)	≤8.8	8.9–21.23	21.3–36.6	36.7–72.9	>72.9	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	1.10 (0.88–1.37)	0.90 (0.72–1.13)	1.04 (0.83–1.31)	0.78 (0.61–1.00)	0.02
All cases/normal controls ^c	1.00	1.03 (0.79–1.35)	0.80 (0.61–1.05)	1.13 (0.85–1.50)	0.80 (0.59–1.08)	0.23
Advanced cases/all controls ^d	1.00	1.01 (0.74–1.38)	0.75 (0.54–1.05)	0.88 (0.64–1.22)	0.61 (0.42–0.88)	0.006
Corn						
Quintile range (g/day)	≤0.5	0.5–5.6	5.7–9.4	9.5–17.8	>17.8	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	1.03 (0.83–1.26)	0.92 (0.72–1.18)	0.95 (0.76–1.19)	0.78 (0.62–0.99)	0.02
All cases/normal controls ^c	1.00	0.92 (0.71–1.20)	0.82 (0.61–1.12)	0.99 (0.74–1.31)	0.64 (0.48–0.86)	0.004
Advanced cases/all controls ^d	1.00	0.98 (0.74–1.32)	0.83 (0.58–1.19)	0.82 (0.60–1.14)	0.78 (0.56–1.10)	0.12
Carrots						
Quintile range (g/day)	≤2.7	2.8–6.5	6.6–12.9	13.0–24.3	>24.3	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.73 (0.58–0.91)	0.66 (0.53–0.82)	0.67 (0.54–0.84)	0.64 (0.51–0.81)	0.01
All cases/normal controls ^c	1.00	0.64 (0.49–0.85)	0.59 (0.44–0.78)	0.68 (0.51–0.90)	0.55 (0.41–0.73)	0.004
Advanced cases/all controls ^d	1.00	0.73 (0.54–0.98)	0.59 (0.43–0.82)	0.57 (0.41–0.79)	0.50 (0.36–0.70)	0.0005
Tomatoes						
Quintile range (g/day)	≤20.0	20.1–39.3	39.4–66.8	66.9–108.1	>108.1	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.99 (0.79–1.25)	1.14 (0.91–1.44)	0.88 (0.69–1.12)	1.07 (0.83–1.38)	0.85
All cases/normal controls ^c	1.00	1.11 (0.83–1.47)	1.35 (1.01–1.80)	0.91 (0.68–1.23)	1.19 (0.87–1.63)	0.73
Advanced cases/all controls ^d	1.00	1.06 (0.76–1.47)	1.07 (0.76–1.50)	1.06 (0.75–1.50)	1.08 (0.75–1.56)	0.78
Tomatoes (cooked)						
Quintile range (g/day)	≤18.3	18.3–35.1	35.3–57.9	58.0–92.7	>92.7	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	1.07 (0.90–1.08)	1.11 (0.88–1.41)	0.79 (0.56–1.12)	0.94 (0.58–1.52)	0.56
All cases/normal controls ^c	1.00	1.00 (0.81–1.25)	1.15 (0.86–1.55)	0.74 (0.48–1.12)	0.97 (0.53–1.77)	0.64
Advanced cases/all controls ^d	1.00	1.12 (0.87–1.44)	1.13 (0.80–1.59)	0.80 (0.48–1.35)	0.96 (0.48–1.93)	0.76
All vegetables						
Quintile range (g/day)	≤101.3	101.4–157.4	157.5–220.0	220.1–324.8	>324.8	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.85 (0.68–1.06)	0.87 (0.69–1.09)	0.81 (0.64–1.03)	0.74 (0.58–0.96)	0.04
All cases/normal controls ^c	1.00	0.86 (0.65–1.14)	0.94 (0.71–1.25)	0.90 (0.68–1.21)	0.71 (0.52–0.96)	0.04
Advanced cases/all controls ^d	1.00	0.85 (0.61–1.17)	0.80 (0.58–1.11)	0.80 (0.57–1.12)	0.67 (0.46–0.96)	0.04
Citrus fruits						
Quintile range (g/day)	≤31.6	31.7–84.0	84.1–149.6	149.7–248.5	>248.5	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	1.19 (0.95–1.50)	1.00 (0.80–1.26)	1.16 (0.92–1.46)	1.15 (0.91–1.45)	0.40
All cases/normal controls ^c	1.00	1.21 (0.92–1.60)	0.93 (0.71–1.23)	1.07 (0.81–1.41)	1.06 (0.80–1.40)	0.95
Advanced cases/all controls ^d	1.00	1.30 (0.94–1.79)	0.93 (0.66–1.30)	1.13 (0.81–1.58)	1.22 (0.88–1.70)	0.45
Papaya						
Quintile range (g/day)	0	>0 ^e				
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.90 (0.72–1.12)				0.34
All cases/normal controls ^c	1.00	0.98 (0.74–1.28)				0.86
Advanced cases/all controls ^d	1.00	0.85 (0.62–1.18)				0.34
All fruits						
Quintile range (g/day)	≤75.3	75.4–151.9	152.0–233.3	233.4–360.9	>360.9	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.88 (0.70–1.11)	1.05 (0.83–1.32)	1.10 (0.88–1.38)	1.01 (0.79–1.28)	0.48
All cases/normal controls ^c	1.00	0.84 (0.63–1.12)	0.95 (0.71–1.26)	1.03 (0.77–1.37)	0.90 (0.67–1.21)	0.91
Advanced cases/all controls ^d	1.00	0.98 (0.70–1.37)	1.11 (0.79–1.55)	1.15 (0.82–1.61)	1.13 (0.80–1.60)	0.36

^a OR (95% CI), adjusted for age, education, ethnicity, geographic area, and calories.

^b Number of cases, 1619; number of controls, 1618.

^c Control subjects with normal PSA values; *n* = 847.

^d See "Materials and Methods" for definition of "advanced"; *n* = 514.

^e Consumption too low for quintiles. ORs and Ps based on intake above *versus* below the median.

Table 4 Prostate cancer risk according to quintiles of intake of legumes

Food item or group	Quintile					P for trend
	1 (low)	2	3	4	5 (high)	
Soyfoods						
Quintile range (g/day)	0	0.1–0.5	0.6–18.0	18.1–39.4	>39.4	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.75 (0.60–0.94)	0.75 (0.55–1.02)	0.85 (0.61–1.19)	0.62 (0.44–0.89)	0.06
All cases/normal controls ^c	1.00	0.81 (0.61–1.08)	0.71 (0.49–1.01)	0.88 (0.59–1.32)	0.64 (0.42–0.98)	0.17
Advanced cases/all controls ^d	1.00	0.65 (0.46–0.92)	0.75 (0.47–1.18)	0.95 (0.58–1.56)	0.59 (0.35–1.00)	0.13
Legumes (excluding soyfoods)						
Quintile range (g/day)	≤2.6	2.7–10.3	10.4–23.1	23.2–51.5	>51.5	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.87 (0.69–1.09)	0.83 (0.66–1.04)	0.87 (0.69–1.10)	0.68 (0.53–0.88)	0.01
All cases/normal controls ^c	1.00	0.84 (0.64–1.11)	0.84 (0.63–1.11)	0.84 (0.63–1.11)	0.62 (0.46–0.86)	0.006
Advanced cases/all controls ^d	1.00	0.94 (0.68–1.30)	0.88 (0.63–1.22)	1.05 (0.75–1.46)	0.73 (0.50–1.07)	0.11
All legumes						
Quintile range (g/day)	≤10.0	10.1–23.7	23.8–43.6	43.7–81.0	>81.0	
OR (95% CI) ^a						
All cases/all controls ^b	1.00	0.89 (0.71–1.10)	0.85 (0.68–1.07)	0.81 (0.64–1.01)	0.62 (0.49–0.80)	0.0002
All cases/normal controls ^c	1.00	0.91 (0.69–1.20)	0.83 (0.63–1.10)	0.77 (0.58–1.02)	0.59 (0.44–0.80)	0.0004
Advanced cases/all controls ^d	1.00	1.02 (0.74–1.41)	1.00 (0.72–1.38)	0.94 (0.67–1.31)	0.74 (0.52–1.06)	0.04

^a OR (95% CI), adjusted for age, education, ethnicity, geographic area, and calories.

^b Number of cases, 1619; number of controls, 1618.

^c Control subjects with normal PSA values; *n* = 847.

^d See “Materials and Methods” for definition of “advanced”; *n* = 514.

statistically significant inverse relationship ($P = 0.04$). With regard to individual vegetables, corn and carrots showed the most suggestive findings. For both vegetables, there is a significant inverse trend, and for carrots, the ORs are statistically significant in all quintiles. Because tomatoes are the only vegetable source of lycopene, this food item was of particular interest. Neither all tomatoes nor cooked forms of tomatoes (from which lycopene absorption is enhanced, because of the usual presence of lipids) show evidence of a protective effect. No other specific vegetables showed suggestive relationships (data not shown).

Neither fruit overall nor citrus fruits as a subgroup show a clear relationship to prostate cancer risk; most ORs are greater than or about equal to 1.0, suggesting, if anything, an adverse rather than protective effect of fruits. Papaya, which is rich in β -cryptoxanthin, also shows no association with prostate cancer risk. This fruit was of interest, because we had found a direct association of prostate cancer with papaya in an earlier case-control study in Hawaii (15).

Because occult malignancy in the prostate occurs at a high frequency among older men in the United States (16), we can assume that a portion of the men in the control group had undetected prostate cancer. Therefore, we repeated the analyses excluding from the controls 107 men who had elevated PSA values (defined in “Materials and Methods”), 162 men who had prior prostate surgery for benign conditions or chemotherapy within the past year for any other cancer and 502 men who had not provided a blood sample. The results are shown in Table 3 as “all cases/normal controls.” For vegetables, the trends are similar to those seen for “all cases/all controls,” although the inverse trend for the cruciferous vegetables is somewhat weaker, and those for corn and carrots are somewhat stronger. For fruits, the trends are unchanged.

In a second restriction, we compared the cases with advanced disease (defined in “Materials and Methods”) with all controls. For vegetables, the inverse trends in this analysis are stronger for the yellow-orange and cruciferous groupings and for carrots in particular, compared with the analyses of all

cases/all controls, and all cases/normal controls. An inverse relationship is now suggested for dark green vegetables as well. For fruits, the trends are again unchanged.

Table 4 shows the findings on legumes. (A list of the individual food items included in legumes is given in the “Appendix.”) For all legumes combined, there is a monotonic inverse trend for all cases/all controls. This trend is slightly more pronounced when the analysis is limited to the normal controls but is not enhanced by restricting the analysis to the advanced cases.

Legumes are sources of exposure to phytoestrogens, including the isoflavonoids found in tofu and other products made from soybeans. Hence, we examined soyfoods and legumes excluding soy products, separately. Legumes exclusive of soy products show an inverse relationship with prostate cancer risk similar to that for all legumes, although the trend is not quite monotonic and is somewhat weaker when the analysis is limited to the advanced cases. Soyfoods also show an inverse relationship to risk, with similar ORs in the highest quintile to those for the other legume groupings. The inverse trend for all cases/all controls is not strengthened for tofu by restricting the analysis to the normal controls or the advanced cases.

We also analyzed the data separately for men <70 years of age versus 70 years and older. The findings were generally very similar for the two age groups.

For the significant inverse associations in Tables 3 and 4 (plus cooked tomatoes), we looked for consistency across the four ethnic groups in the study. Because of the smaller number of subjects in the individual ethnic groups, these analyses were conducted using tertiles. Table 5 shows the results for all cases/all controls. The findings were generally very similar for all cases/normal controls and for advanced cases/all controls (data not shown).

As seen in Table 5, for yellow-orange vegetables, higher intake is associated with lower prostate cancer risk in all ethnic groups, and the trend is statistically significant in the Japanese. For cruciferous vegetables, on the other hand, the inverse relationship is only apparent in the Japanese and Chinese ethnic

hand, a study in Japan found an inverse association with green-yellow vegetables (21); another study in Canada found an inverse association with green vegetables, cruciferous vegetables, and tomatoes (22); a study in the United States reported an inverse association with carrots (23); and a study in South Africa found inverse associations with carrots, cabbage, and spinach (24). A study in China found greater intake of carotene-rich vegetables by controls than by cases, although the authors stated that the effect disappeared after adjustment for other dietary factors (25).

The findings from prospective cohort studies are also inconclusive. Two studies found no association for total vegetables (26, 27), and one study found no association for cruciferous vegetables in particular (28). A study in Japan reported a protective effect of green-yellow vegetables in men <75 years of age (29), whereas a study of Japanese men in Hawaii (30) reported an increased risk in men with higher seaweed consumption. Two cohort studies found an inverse association with the consumption of tomatoes but not of total vegetables or of other specific vegetables (31, 32). A recent study from the Netherlands (33) found no overall association with vegetable intake.

Because the dark green and cruciferous vegetable groupings overlap substantially in the food items they contain (see "Appendix"), our inverse findings for yellow-orange and cruciferous vegetables are consistent with the inverse association for green-yellow vegetables reported by Hirayama (29) and Ohno *et al.* (21) in Japan and for green and cruciferous vegetables reported by Jain *et al.* (22) in Canada. Our finding of an inverse association with carrots agrees with those of Schuman *et al.* (23) and Walker *et al.* (24). Explanations for the associations with specific vegetables must be speculative, because the present analysis was not designed to examine specific food constituents. Although the association with carrots could reflect their substantial β -carotene content, it could also implicate α -carotene, because in our study population, carrots contributed <10% of the total β -carotene intake from foods, whereas they contributed ~60% of the intake of α -carotene. Alternatively, the finding for carrots could reflect some other constituent of this food, such as phytosterols, that potentially could protect against prostate cancer. The inverse association we found for corn could reflect a beneficial effect of lutein, which is present in significant amounts in this food. Corn also contains small amounts of α -carotene, β -carotene, folic acid, and other potentially beneficial microconstituents.

Tomatoes were of particular interest in this study because they are the major source of lycopene in the diet (other sources include watermelon, grapefruit, and guava). Lycopene is a potent antioxidant and is widely but not uniformly distributed in human tissues, including the prostate (34). In one analysis (35), concentrations of lycopene were highest among the diverse carotenoids found in human prostate tissue. Thus, an anticarcinogenic function of this carotenoid in the prostate is plausible. However, current epidemiological literature related to this issue is inconsistent. Of six case-control studies, four found no statistically significant inverse association of prostate cancer with the consumption of tomatoes (16, 20, 23, 36) or with estimated lycopene intake (36). The fifth study found no inverse association of total prostate cancer with raw or cooked tomatoes but did see an inverse association of advanced prostate cancer with raw (but not cooked) tomatoes (19). The sixth study (22) found a statistically significant inverse trend with tomatoes ($P = 0.04$) but not with estimated intake of lycopene. In the present study, we were careful to estimate the intake of tomatoes from all sources in the diet, including the tomato in mixed dishes, such

as stews. Because of the ethnic diversity of the study, we had a substantial range in intakes (ethnic-specific means from 42.6–101.0 g/day), which should have increased our potential to demonstrate a clear inverse association. We found no overall association with total tomatoes or cooked tomatoes nor with lycopene-containing fruits or a combination of all lycopene foods (data not shown). The ethnic-specific analysis for tomatoes was inconsistent. Most other studies of prostate cancer and diet have been in populations of white men. In one other study that included both African-American and white men (19), the investigators found no statistically significant associations of raw or cooked tomatoes with total prostate cancer in either African-American or white men, although a nonsignificant inverse trend for raw (but not cooked) tomatoes was seen for both groups in an analysis restricted to advanced (regional/distant) cases.

Of three cohort studies that reported on dietary tomato consumption, two found a significant inverse association (31, 32) and one (33) found no association. Finally, three studies examined prostate cancer risk in relation to lycopene levels in blood, based on prediagnostic stored specimens. Two of these investigations (37, 38) found an inverse relationship [although the reduction in risk was statistically significant in only one of these studies (38), and only among the subset of aggressive cases], and the third (39) found no association.

There is little epidemiological evidence for a protective effect of fruits against prostate cancer. In fact, several studies have suggested a direct association. In an earlier case-control study in Hawaii, we reported a positive association with total vitamin A intake, largely attributed to consumption of papaya (15, 40), although this finding was not reproduced in the present study, even when the analysis was restricted to the cases and controls from Hawaii (data not shown). In a case-control study in Japan (21), fruit consumption was associated with a moderate increase in prostate cancer risk. A recent case-control study from Canada (22) reported a statistically significant positive association between prostate cancer and the intake of total fruit, citrus fruit, and fruit other than citrus. Fruits and fruit juices as a single category were significantly positively associated with prostate cancer in another recent Canadian case-control study (20). Fresh fruit showed no association with prostate cancer in a case-control study in Italy (18), and the mean weekly consumption of total fruits was similar for cases and controls in a study conducted in China (25). In a recent multicentered case-control study of African American and white men in the United States, fruit as a category showed no relationship to risk in either ethnic group, although when the analysis was restricted to advanced cases of prostate cancer, there was a nonstatistically significant inverse relationship in the whites (19).

Among cohort investigations, no clear association with total fruit intake was seen in five studies (26–28, 31, 32). In a subsequent report on one of these cohorts (32), a protective effect against advanced prostate cancer was seen for fruits; this finding was accounted for by fructose intake (41). Two other cohorts (30, 33) found an increased risk associated with total fruit intake; the result was statistically significant in one of these studies (33). One cohort study (31) found a weak inverse association for dried fruits (raisins, dates, and others); another (30) found a statistically significant increase in risk for citrus fruits. Thus, at the present time, evidence in support of a beneficial role of fruits for prostate cancer is very limited, and the data are inconsistent.

Few past epidemiological studies of prostate cancer have reported on legumes (pulses) in particular. In a case-control study in Minnesota (23), a weak inverse association was found

for consumption of peas and beans. Inverse associations were also seen for total legumes, baked beans, garden peas, and green/broad/runner beans but not dried lentils/beans/peas in a case-control study in England (36). One recent case-control study in Canada (20) found no inverse association with lentils/baked beans but a weak inverse trend for tofu or soybean (dichotomized as none *versus* some per week). Another Canadian case-control study (22) found a statistically significant inverse association with intake of beans/lentils/nuts/seeds as a food group. Although the mean weekly consumption of soy was higher among controls than cases of prostate cancer in a study in China, the difference was not statistically significant; the intake of other legumes did not differ between the two groups (25).

Three cohort studies have reported protective associations for legumes. In a study among Seventh Day Adventists, statistically significant inverse associations were found with intake of peas/beans/lentils (31) and with the consumption of soy milk (42). In a cohort of Japanese men in Hawaii, a nonstatistically significant inverse association was reported for consumption of tofu (30). In a Dutch cohort, a statistically significant inverse association was found for legumes as a group (33).

Legumes have been of interest in nutritional epidemiology primarily for their high content of fiber and, more recently, for their phytoestrogen content. Phytoestrogens are plant constituents that have mild estrogenic properties. Because estrogens may lower the risk of prostate cancer and are used in prostate cancer therapy, there is a good rationale for hypothesizing an inverse relationship of phytoestrogens to prostate cancer. Soybeans and many products made from soy, such as tofu, are rich in a class of phytoestrogens known as isoflavones (other classes of phytoestrogens include the coumestans and lignans). The main isoflavones found in soy include genistein, diadzein, and glycitein (43, 44). In our analysis, we found evidence of a protective effect of legumes whether or not we restricted the analysis to soy products. This suggests the possibility that the effect may reflect some general, more widespread, component of legumes. Another important constituent of legumes that could account for the inverse association is fiber, which has not been well studied with regard to prostate cancer (4). Other bioactive constituents of legumes that have anticarcinogenic properties and could potentially account for a protective effect include saponins (45, 46), protease inhibitors (45, 47), inositol hexaphosphate (45), γ -tocopherol (48), and phytosterols (49). It is also possible that the combination of several different constituents of legumes is most effective in reducing prostate cancer risk.

Our analyses based on control subjects without elevated PSA levels is a unique feature of this study. On the one hand, these analyses enabled us to remove from the controls men who may have harbored undetected cancers, a potential source of misclassification, although because the PSA test is not specific for cancer, we undoubtedly excluded many men without subclinical disease. Furthermore, to exclude men from the controls for these analyses, a blood sample had to be available. In fact, most of the men excluded from the controls for the restricted analyses were those who provided no blood sample (502 men), rather than those with an elevated PSA value (107 men). We compared the men who did and did not donate blood on a number of variables. Men who donated blood were slightly younger on average (by 2.7 years) and included a higher proportion of whites and Japanese and a lower proportion of African-Americans and Chinese compared with the non-donor group; however, the two groups did not differ with respect to dietary intakes (calories, fat, vegetables, fruit, and legumes),

either with or without adjustment for age and race. Compared with the non-donors, the donor group also contained a lower proportion of men who reported a history of an enlarged prostate (14% *versus* 27%) and a higher proportion of men who smoked (22% *versus* 11%) or consumed alcohol (67% *versus* 56%) in the preceding year; none of these variables was associated with prostate cancer risk in this study.

We do not know to what extent cases and controls may have differed in their screening practices and thus to what extent more intensive screening could have contributed to the detection of men in the cases series. If the cases as a group had been more heavily screened and if screening behavior were associated with dietary practices such that men who got screened had more healthful diets, then the ORs we found might well underestimate the true effect. On the other hand, limiting the analysis to the subset of PSA-normal controls, when screening may not have occurred at the same rate in the case and control groups, could have introduced an unknown selection bias. Thus, we present our results both with and without exclusions from the control group. Because the non-donor men did not differ in significant ways from the donors, as noted above, and because the proportion of men excluded for elevated PSA levels was relatively small (7%), the similarity of the results for the two control comparisons is perhaps not unexpected.

A strength of this study was the inclusion of ethnic groups at high, intermediate, and low levels of risk for prostate cancer. These groups also added dietary diversity, enabling us, for example, to examine the relationship of tofu to prostate cancer, because the Asian groups and many of the whites in Hawaii consume these foods regularly. However, there are some limitations that must also be recognized:

(a) The study was retrospective, and cases may have recalled their diets differently from controls, leading to recall bias. We made a point of establishing comparable reference periods for the diets of the cases and controls, and it is noteworthy that the cases did not systematically report less healthful dietary practices than the controls. We compared the findings for the cases who were interviewed within 1 year of diagnosis with those who were interviewed after a longer interval. For the vegetable groupings that showed an inverse relationship to prostate cancer risk (yellow-orange and cruciferous), the trends were somewhat stronger for the group interviewed within 1 year, although the overall patterns were similar. For legumes, the inverse relationships for both subgroups (soyfoods and "other legumes") were almost identical for the two intervals.

Although only a small proportion of cases (9%) were interviewed via surrogates (mostly wives), we repeated the analyses excluding these cases, and the results were unchanged. This agrees with our earlier report (50) that the information collected from wives regarding their husbands' dietary, drinking, and smoking habits was closely correlated with the information collected from the subjects themselves. Of course, measurement error is a concern in all dietary recall studies. If the errors are nondifferential between cases and controls, attenuation of the ORs is the general, but not certain, result. We instituted some measures to reduce measurement error in dietary data collection, such as intensive training and monitoring of the interviewers and the use of a validated dietary assessment method.

(b) A second consideration is selection bias. Although response rates were acceptably high (63–79%) among cases in all four ethnic groups and among controls in three ethnic groups, the response rate among African-American controls was only 45%. The latter rate, especially, could have introduced

selection bias, although the findings for the African-American men were generally consistent with those of the other groups. Lower response rates is one consequence of designing a study to be population-based and to include members of lower socioeconomic strata.

(c) A third consideration is that men who consume greater quantities of vegetables may also consume more legumes (and *vice versa*), so that the findings of the present study might simply reflect the benefits of a more heavily plant-based diet. Such a diet would contain lower amounts of the red meats and other sources of saturated fat that were positively associated with prostate cancer in our earlier report (5). However, the mean intake of legumes by the cases in all ethnic groups was lower than among controls (Table 1), whereas the mean intake of fruits and vegetables was higher in the African-American and white cases. Also arguing against this interpretation is the fact that the correlations between the various vegetable groupings and legumes (Table 2) were weak in all instances ($r \leq 0.3$).

In conclusion, this study found an inverse association between prostate cancer and the intake of legumes and certain categories of vegetables among white, African-American, and Asian men in the United States and Canada. The results suggest that a diet with higher intakes of these foods may lower the risk of prostate cancer in these populations.

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Appendix: Foods Included in the Vegetable, Fruit, and Legume Groupings

Dark Green Vegetables. Broccoli, chard, chicory greens, chili peppers, green mustard cabbage, green peppers, jalapeno peppers, lettuce (romaine, cos, and looseleaf), mustard greens, ong choy, pak choy, parsley, spinach, taro leaves, turnip greens, and watercress.

Yellow-Orange Vegetables. Carrots, pumpkin, sweet potatoes, and winter squash.

Cruciferous Vegetables. Broccoli, Brussels sprouts, green mustard cabbage, head cabbage, mustard greens, pak choy, red cabbage, turnip greens, watercress, and won bok.

Other Vegetables. Asparagus, bamboo shoots, celery, corn, green beans, lettuce (head), lima beans, mushrooms, onions, sprouts, peas, summer squash, and tomatoes.

Citrus Fruits. Grapefruit and grapefruit juice, mandarin oranges, oranges and orange juice, and tangerines.

Other Fruits. Apricots, cantaloupe, guava and guava juice, mango, nectarines, papaya, passion fruit, peaches, prunes, and watermelon.

Legumes. Aburage, beans (azuki, black, garbanzo, green, kidney, lima, mung, navy, pinto, red, white, and yellow), black-eyed peas, miso, peas, soy beans, and tofu.

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Vegetables, Fruits, Legumes and Prostate Cancer: A Multiethnic Case-Control Study

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