Fruit and Vegetable Intakes and Prostate Cancer Risk

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Background: **There is extensive and consistent evidence that high fruit and vegetable intakes are associated with decreased risks of many cancers, but results for prostate cancer risk have been inconsistent. We studied the associations of fruit and vegetable intakes with prostate cancer risk in a population-based, case–control study of men under 65 years of age.** ***Methods:*** **Case participants were 628 men from King County (Seattle area), WA, who were newly diagnosed with prostate cancer. Control participants were 602 men recruited from the same underlying population and frequency matched to case participants by age. Self-administered food-frequency questionnaires were used to assess diet over the 3- to 5-year period before diagnosis or recruitment. Daily nutrient intakes were calculated by use of a nutrient database with recently updated analytic values for carotenoids. Odds ratios for prostate cancer risk associated with foods and nutrients were calculated by use of unconditional logistic regression.** ***Results:*** **No associations were found between fruit intake and prostate cancer risk. The adjusted odds ratio (ORs) for the comparison of 28 or more servings of vegetables per week with fewer than 14 servings per week was 0.65 (95% confidence interval [CI] = 0.45–0.94), with a two-sided *P* for trend = .01. For cruciferous vegetable consumption, adjusted for covariates and total vegetable intake, the OR for comparison of three or more servings per week with less than one serving per week was 0.59 (95% CI = 0.39–0.90), with a two-sided *P* for trend = .02. The OR for daily intake of 2000 μg or more lutein plus zeaxanthin compared with an intake of less than 800 μg was 0.68 (95% CI = 0.45–1.00).** ***Conclusion:*** **These results suggest that high consumption of vegetables, particularly cruciferous vegetables, is associated with a reduced risk of prostate cancer. [J Natl Cancer Inst 2000;92:61–8]**

Evidence supporting the protective effects of high fruit and vegetable consumptions on the risks of many cancers is extensive and consistent, but existing studies of fruit and vegetable intakes and prostate cancer are contradictory. A comprehensive review of the literature, which is beyond the scope of this report, can be found elsewhere *(1).* Of eight studies *(2–9)* that have reported results for total fruit or vegetable consumption and prostate cancer risk, only one *(8)* found a statistically significant protective association. Case–control and cohort studies *(2,4,6,7,10–20)* have found null, increased, and protective effects on risk of prostate cancer for specific fruits and vegetables. For example, studies examining cruciferous vegetables have found statistically significant protective effects *(16),* nonsignificant protective effects *(12,18),* and no associations *(4,6,10,13).*

In many previous studies *(2–20)* of fruits and vegetables and prostate cancer risk, sample sizes were quite small, measures of fruit and vegetable intakes were not comprehensive, and analyses were not controlled for important confounders, such as age or fat intake. Additional, better designed studies are needed to resolve the inconsistencies in this literature.

We studied the associations of fruit and vegetable intakes with prostate cancer risk in a population-based, case–control study of men aged 40–64 years. This study differs from most earlier studies in several ways. Dietary assessment was based on a comprehensive food-frequency questionnaire (FFQ), the nutrient database used recently updated analytic values for carotenoids, and statistical methods were used to separate effects of total fruit and vegetable intakes from the effects of specific fruits and vegetables.

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See "Notes" following "References."

METHODS

Data were from a population-based, case–control study of risk factors for prostate cancer. The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and written informed consent was obtained from all of the participants.

Eligible case participants were white and black male residents of King County (Seattle area), WA, who were aged 40–64 years and who were newly diagnosed with histologically confirmed prostate cancer between January 1, 1993, and December 31, 1996. Case participants were identified from the Seattle–Puget Sound Surveillance, Epidemiology, and End Results (SEER)[1] cancer registry. (Only case participants with a residential telephone were eligible because control participants were selected by use of random-digit dialing.) Because the emphasis was on recruiting younger men, only a random sample of 75% of the prospective case participants aged 60–64 years were recruited. Of the 917 case participants selected for the study, 753 (82%) were interviewed. Reasons for nonresponse were physician refusal to allow contact (2.6%), participant refusal (13%), inability to locate (1.5%), illness (0.4%), and death (0.2%).

Control participants were identified by use of random-digit dialing. They were recruited evenly throughout the ascertainment period for case participants and were frequency matched to case participants by age (same 5-year group). Of the 21 116 residential numbers contacted, 94% provided household census data. Of the 1025 eligible men identified, 941 (92%) agreed to receive mailed information about the study, and 703 of those (75%) were interviewed. Reasons for nonresponse were participant refusal (24%), loss to follow-up (<1%), and illness (<1%).

Clinical information was abstracted from the SEER registry. Aggressive tumors were defined as either stage C or D [Whitmore–Jewett system *(21)*] or as histopathologic grade 8–10 [Gleason system *(22)*].

Participants completed in-person interviews conducted by trained male interviewers. Information collected included demographic characteristics, height and weight, family history of prostate cancer, and 5-year history of screening by use of prostate-specific antigen (PSA) measurements and digital rectal examination. A calendar of life events was used to enhance recall. For case participants, time-sensitive questions used diagnosis dates as reference dates. For control participants, reference dates were randomly assigned from dates that approximated the distribution of case participants' diagnosis dates.

After the interview, participants were given the FFQ and asked to complete it at home and return it by mail. The FFQ asked about the usual consumption of 99 food items, including 12 fruit items and 21 vegetable items, over the 3- to 5-year period preceding the reference date. Each food item had nine options for frequency (ranging from "never or less than once per month" to "2+ per day" for foods and "6+ per day" for beverages) and three options for portion size. The FFQ had 19 questions about food purchasing and preparation practices and two summary questions that asked about the frequency of consuming all servings of fruit (excluding juice) and all vegetables (excluding salad or potatoes) (ranging from "less than one per week" to "5+ per day").

FFQs were completed by 654 case (87%) and 625 control (89%) participants. Participants whose calculated daily energy intakes were less than 800 kcal (23 case and 21 control participants) or greater than 5000 kcal (three case and two control participants) were excluded because their FFQs were considered unreliable. The final sample was composed of 628 case participants and 602 control participants with reliable food-frequency data.

Total fruit and vegetable consumptions were estimated in two ways. In the first, we used the method of the National Cancer Institute-sponsored 5-a-Day for Better Health community studies: We added answers to the FFQ's summary questions about frequencies of fruit (excluding juices) and vegetable (excluding salad or potatoes) consumptions to answers to the FFQ's questions about consumptions of juice, salads, and potatoes (not fried) *(23)*. This method reduces the respondents' tendency to overestimate consumption of categories of foods when there are many items in a related food group *(24)*.

The second method was simple summation. We added intakes of all fruit or vegetable items listed in the FFQ. Vegetables included potatoes (not fried), beans, bean soups, vegetable soups, and 17 specific vegetables or groups of vegetables. We also calculated a separate category not included in total vegetables, "tomatoes from pizza and spaghetti sauce," by adding two food items from the FFQ: pizza and spaghetti with tomato sauce.

For analyses of specific vegetable and fruit groups, we calculated servings per week of cooked tomatoes, raw tomatoes, carrots, cruciferous vegetables, beans, green leafy vegetables, "other vegetables" (string beans and green beans, peas, corn, summer squash, winter squash, onions and leeks, lettuce, mixed lettuce salad, sweet potatoes, other potatoes [not fried], bean soups, and vegetable soups), citrus fruits, citrus juice, and "other fruits" (apples and pears; bananas; peaches, nectarines, and plums; cantaloupe; other melon; apricots; other dried fruit; strawberries; any other fruit; and other fruit juices).

Daily energy, fat, vitamin C, and carotenoid intakes were calculated by use of algorithms developed at the Fred Hutchinson Cancer Research Center *(25)* and a nutrient database from the University of Minnesota Nutrient Data System *(26)* that incorporated updated data from the U.S. Department of Agriculture on carotenoid content of fruits and vegetables *(27)*. The 19 questions on the FFQ that asked about food purchasing and preparation practices were used to adjust nutrient calculations *(25,28)*. Carotenoid intake exclusive of lycopene was estimated because both dietary intake and serum concentration of five of the major carotenoids (β-carotene, α-carotene, β-cryptoxanthin, lutein, and zeaxanthin) are intercorrelated, while lycopene levels are relatively independent *(29)*.

Geometric mean intakes of vegetables, fruits, and nutrients were calculated for case participants and control participants because the distributions of these variables are log normal. Values were log transformed for the purposes of calculations but back transformed to original units for ease of interpretation.

Unconditional logistic regression was used to calculate odds ratios (ORs) for risk of prostate cancer associated with nutrients and foods, both with and without adjustment for eight covariates: age (categorized in 5-year groups), race (white or black), family history of prostate cancer (none, in first-degree relatives, or in second-degree relatives only), education (≤12, 13–15, 16, or ≥17 years), body mass index (weight in kilograms/[height in meters]^2) (18–23, 24–26, 27–29, or ≥30 kg/m^2), number of screening PSA tests within 5 years of reference date (0, 1–2, 3–4, or ≥5), and dietary intakes of energy and fat (both log transformed). We categorized individual fruit and vegetable intakes into ranges that reflect common dietary patterns (<1, 1–2.9, or ≥3 times per week) and categorized nutrients roughly into quartiles based on the distributions in the entire sample. ORs associated with specific vegetable or fruit groups were adjusted for total vegetable or fruit intake and for the eight covariates. The interpretation of these models is whether or not substituting a particular vegetable or fruit for other vegetables or fruits while keeping total vegetable or fruit intake constant changes disease risk.

Tests for trends associated with increased intake used the method of Breslow and Day *(30)*. Polytomous logistic regression was used for analyses that stratified case participants into those with aggressive and those with nonaggressive tumors. A two-sided probability of <.05 was used as the criterion of statistical significance.

RESULTS

Table 1 gives demographic characteristics, family history of prostate cancer, and PSA test history of case and control participants and lists the stage of disease at diagnosis for case participants. The demographics of the study sample were consistent with those of the underlying population of the King County (Seattle area), WA. More than 60% of the study participants were under age 60 years, and more than 50% were college graduates. Case participants were more likely than control participants to have a family history of prostate cancer, to be black, or to have had PSA screening tests. (PSA tests done at the time of diagnosis of prostate cancer are not included in the data in this table.) The majority of case participants had localized disease confined to the prostate (stage B).

Table 2 compares fruit and vegetable consumptions and energy, fat, vitamin C, and carotenoid intakes of case and control participants. Fruit and vegetable consumptions are reported in servings per week, both as total consumption (calculated two ways) and divided into categories. Servings per week were the highest for raw tomatoes, cruciferous vegetables, and carrots. Energy, fat, vitamin C, and carotenoid intakes are reported in the indicated units on a daily basis.

Table 3 gives associations of fruit and vegetable intakes with prostate cancer risk. There were no statistically signifi-

Table 1. Demographic and health-related characteristics of case and control participants

Characteristic	Case participants, % (n = 628)	Control participants, % (n = 602)
Age, y		
40–49	5.1	7.1
50–54	19.1	18.4
55–59	36.0	38.5
60–64	39.8	35.9
Race		
White	95.5	98.5
Black	4.5	1.5
Family history of prostate cancer		
None	72.3	84.4
First degree	19.3	10.1
Second degree only	8.4	5.5
Education, y		
⩽12	27.2	21.9
13–15	20.4	22.8
16	28.3	28.1
⩾17	24.0	27.2
Body mass index, kg/m^2*		
18–23	23.7	21.8
24–26	37.7	34.7
27–29	21.7	25.3
⩾30	16.9	18.3
No. of PSA tests within previous 5 y†		
None	28.7	66.6
1–2	33.8	19.1
3–4	20.1	8.6
⩾5	17.7	5.7
Stage at diagnosis‡		
A	14.5	
B	57.0	Not applicable
C	18.8	
D	7.0	
Unknown	2.7	

*Body mass index = weight in kilograms/[height in meters]^2.

†Prostate-specific antigen (PSA) tests done in conjunction with prostate cancer diagnoses of case participants are not included.

‡*See (21)* for information on staging.

cant associations of fruit intake with prostate cancer risk. A modest, not statistically significant, decreased risk was associated with total fruit consumption calculated by the 5-a-Day method (but not when simple summation was used). In contrast, there were stronger protective effects for total vegetable consumption (calculated either by the 5-a-Day method or by simple summation). In models adjusted for covariates, there were significant linear trends, with 35%–48% reductions in risk in the highest intake categories.

When data for individual vegetable groups were adjusted for covariates, there were statistically significant protective effects for the highest intake categories of cruciferous vegetables, carrots, and "other vegetables" and statistically significant trends for cruciferous vegetables and carrots. Only the association of cruciferous vegetables remained statistically significant after controlling for total vegetable intake.

We also analyzed the data excluding potatoes because of their low nutrient density. The results did not change.

We examined the effects of tomatoes and tomato products. The unadjusted ORs for cooked tomatoes are similar to those for "other vegetables," but the ORs adjusted for covariates were weaker for cooked tomatoes than for "other vegetables." When controlled for total vegetable intake, effects for cooked tomatoes were further reduced. For the highest levels (controlled for covariates but not for total vegetable consumption), ORs of prostate cancer were 1.14 (95% confidence interval [CI] = 0.73–1.78) for tomatoes from all sources and 1.01 (95% CI = 0.61–1.68) for tomatoes from pizza and spaghetti sauce. No trends in ORs across levels of intake were apparent for either of these two food categories.

Associations of estimated intakes of vitamin C and carotenoids, nutrients found in fruits and vegetables, with prostate cancer risk are shown in Table 4. There were weak, not statistically significant trends for reduced risk, with increased consumption of total carotenoids (excluding lycopene), α-carotene, β-carotene, lutein plus zeaxanthin, and vitamin C.

We completed several additional analyses to further explore these findings. Associations of fruit, vegetable, and nutrient intakes with prostate cancer risk did not differ by family history (prostate cancer in a first-degree relative compared with others). For the highest category of total vegetable intake (simple summation), the ORs were 0.71 (95% CI = 0.44–1.15) for aggressive tumors and 0.62 (95% CI = 0.41–0.93) for other tumors. For the highest category of cruciferous vegetable intake, controlled for total vegetable intake, ORs were 0.76 (95% CI = 0.43–1.33) for aggressive tumors and 0.52 (95% CI = 0.33–0.84) for other tumors.

We examined whether our results were markedly influenced by the low proportion of PSA screening in control participants by completing analyses by use of data from the 149 control participants (25% of the original control group) who had had a PSA test within 12 months of the reference date. Although there was some irregularity because of small sample sizes, results paralleled those from the total sample. The ORs were 0.57 (95% CI = 0.35–0.93) for the highest category of total vegetable intake (simple summation) and 0.41 (95% CI = 0.23–0.72) for the highest category of cruciferous vegetable intake controlled for total vegetables.

Discussion

The primary findings from this study were statistically significant protective effects on prostate cancer risk for both total and cruciferous vegetable consumption. When total vegetable intake was computed by simple summation, men consuming 28 or more servings of vegetables per week showed a 35% decreased risk for prostate cancer when compared with those eating fewer than 14 servings per week. There was also a 41% decreased risk among men eating three or more servings of cruciferous vegetables per week compared with those eating less than one serving per week, even after controlling for total vegetable intake. Our interpretation of these results is that the sub-

Table 2. Servings of fruits and vegetables per week and nutrients per day in case and control participants*

	Case participants	Control participants
Total fruit, 5-a-Day method	7.0 ± 5.8	7.2 ± 5.9
Total fruit, simple summation	12.2 ± 9.9	11.9 ± 9.5
Citrus fruit†	1.0 ± 1.2	1.0 ± 1.2
Citrus juice‡	2.1 ± 2.5	2.1 ± 1.9
Other fruit	8.4 ± 7.0	8.1 ± 6.6
Total vegetables, 5-a-Day method	11.9 ± 6.8	12.3 ± 7.2
Total vegetables, simple summation	17.9 ± 11.2	18.7 ± 12.0
Cooked tomatoes§	0.8 ± 0.9	0.9 ± 1.0
Raw tomatoes	1.3 ± 1.3	1.3 ± 1.4
Cruciferous vegetables‖	1.6 ± 1.6	1.8 ± 1.8
Carrots	1.0 ± 1.1	1.1 ± 1.2
Beans	0.6 ± 0.6	0.7 ± 0.7
Green leafy vegetables¶	0.3 ± 0.5	0.3 ± 0.5
Other vegetables	11.7 ± 7.4	11.8 ± 7.4
Tomatoes from pizza and spaghetti sauce	1.2 ± 1.0	1.2 ± 0.9
Energy, kcal	1844 ± 719	1808 ± 669
Fat, g	74.4 ± 37.2	72.2 ± 36.7
Vitamin C, mg	84.6 ± 47.1	86.4 ± 47.2
Total carotenoids except lycopene, μg	4769 ± 2752	4964 ± 2894
Total carotenoids, μg	11 848 ± 6173	11 967 ± 6331
α-Carotene, μg	472 ± 378	512 ± 399
β-Carotene, μg	2921 ± 1677	3071 ± 1757
β-Cryptoxanthin, μg	19.9 ± 22.2	20.8 ± 23.1
Lutein and zeaxanthin, μg	1211 ± 796	1260 ± 868
Lycopene, μg	2058 ± 1400	2058 ± 1544

*Geometric mean ± standard deviation values back-transformed into original units.
†Oranges, grapefruit, or tangerines (not juice).
‡Orange juice, grapefruit juice, or vitamin C-enriched fruit drinks.
§Cooked tomatoes, tomato sauce, and salsa.
‖Broccoli, coleslaw, cabbage, sauerkraut, Brussels sprouts, and cauliflower.
¶Cooked greens (spinach, mustard greens, turnip greens, collards, etc.).

stitution of cruciferous vegetables for other vegetables, while keeping total vegetable intake constant, significantly reduces prostate cancer risk.

The statistical model we used is similar to that used in nutritional epidemiology to examine the effect of an individual macronutrient while controlling for total energy intake *(31)*. We believe that this is the most appropriate statistical model to test for an effect of a specific vegetable group, independent of an effect of vegetables *per se*. It seems likely that the significant or nearly significant associations of carrots, "other vegetables," and cooked tomatoes in models not controlled for total vegetables are due to their contributions to total vegetable intake rather than to specific protective effects of the individual vegetables or vegetable group.

Of the nutrients analyzed, only the association between lutein plus zeaxanthin and prostate cancer risk was close to statistical significance. (Because of the limitations in food composition data, we were unable to analyze lutein and zeaxanthin separately.) Lutein is a carotenoid found in high concentrations in cruciferous and green leafy vegetables; it has been used as a biomarker of vegetable intake *(29,32)*. The 32% reduced risk of prostate cancer associated with daily intake of 2000 μg or more of lutein plus zeaxanthin (compared with consumption of <800 μg) provides a plausible biologic explanation for a protective effect of vegetables with high concentrations of these carotenoids. Lack of a statistically significant protective effect for green leafy vegetables may be because of their low consumption in this population.

The protective effect of cruciferous vegetables is consistent with a proposed role for glutathione *S*-transferase (GST) activity in protecting against prostate cancer. GSTPi isoenzymes (the suffix indicates the locus at which these enzymes are encoded) are phase II detoxification enzymes that inactivate carcinogenic electrophiles and organic hydroperoxides and protect cells from DNA-damaging agents *(33,34)*. They are the most abundant GST in human prostate tissue; however, they are absent in 95% of sporadic prostate adenocarcinomas *(33,34)*. Experimental studies *(35–40)* show that indoles and isothiocyanates, which are products of the hydrolysis of glucosinolates found in cruciferous vegetables, inhibit tumorigenesis by inducing GSTPi isoenzymes. It is, therefore, plausible that inducing GSTPi activity by consuming cruciferous vegetables affords protection against environmental and endogenous carcinogenesis associated with the development of prostate cancer.

Recent reports have associated tomato products with decreased risks of prostate *(41–43)* and other *(44)* cancers. Our data showed a not statistically significant 27% reduced risk of prostate cancer associated with consuming three or more servings of cooked tomatoes per week. The reduction in risk decreased to 10% (not statistically significant) after controlling for total vegetable intake. We did not find any association of lycopene intake and prostate cancer risk. Our results are similar to those of four studies that found no association between either tomato consumption or lycopene intake and risk of prostate cancer *(19,20,45,46)*. None of the studies *(9,10,17,42)* reporting protective or null associations for lycopene or tomato products have controlled for total vegetable consumption. Our judgment is that the literature on the relationships of lycopene and tomato products with prostate cancer risk remains inconclusive *(43,44)*.

This study has several limitations. As in any case–control design that assesses exposure after onset of disease, differential dietary recall between case and control participants could bias results. At the time of this study, no media attention was focused on tomato or vegetable intakes and prostate cancer risk. However, national programs, such as 5-a-Day for Better Health, may have increased the public's awareness of the importance of fruits and vegetables for good health and inadvertently affected participants' responses to the FFQ. Control participants may also have been a biased sample of men who were more interested in health and more likely to have diets high in fruits and vegetables. However, that there was no difference in fruit intake between case and control participants is some evidence against this bias. Finally, there are inherent limitations in the accuracy of FFQs, which require participants to estimate their usual dietary patterns over a period several years previously *(47)*.

The widespread use of PSA screening

Table 3. Odds ratios of prostate cancer associated with servings of fruits and vegetables

Servings per week	No. of participants		Odds ratio (95% confidence interval)		
	Case	Control	Unadjusted	Adjusted for covariates*	Adjusted for covariates* + total fruits or vegetables†
Total fruit, 5-a-Day method					Not applicable
<3.5	120	109	1.00 (referent)	1.00 (referent)	
3.5–6.9	167	167	0.91 (0.65–1.27)	0.94 (0.64–1.37)	
7–13.9	212	182	1.06 (0.76–1.47)	0.96 (0.66–1.39)	
⩾14	129	144	0.81 (0.57–1.16)	0.80 (0.53–1.23)	
P for trend‡			.47	.38	
Total fruit, simple summation					Not applicable
<7	128	133	1.00 (referent)	1.00 (referent)	
7–13.9	206	190	1.13 (0.82–1.54)	1.19 (0.84–1.69)	
14–20.9	143	138	1.08 (0.77–1.51)	1.07 (0.73–1.57)	
⩾21	151	141	1.11 (0.80–1.56)	1.07 (0.72–1.60)	
P for trend‡			.65	.96	
Citrus fruit					
<1	347	334	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–2.9	167	152	1.11 (0.85–1.45)	1.09 (0.81–1.46)	1.07 (0.79–1.45)
⩾3	114	116	0.97 (0.72–1.31)	0.93 (0.66–1.30)	0.89 (0.60–1.31)
P for trend‡			.84	.81	.70
Citrus juice					
<1	214	201	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–2.9	126	137	0.96 (0.70–1.30)	0.82 (0.58–1.15)	0.81 (0.56–1.15)
⩾3	288	264	1.09 (0.85–1.40)	1.00 (0.75–1.35)	1.00 (0.73–1.38)
P for trend			.79	.91	.96
Other fruit					
<3.5	98	96	1.00 (referent)	1.00 (referent)	1.00 (referent)
3.5–6.9	129	139	0.91 (0.63–1.32)	0.89 (0.59–1.35)	0.89 (0.59–1.36)
7–13.9	230	214	1.05 (0.75–1.48)	0.95 (0.65–1.39)	0.95 (0.62–1.45)
⩾14	171	153	1.10 (0.77–1.56)	0.99 (0.65–1.50)	0.99 (0.54–1.80)
P for trend‡			.39	.91	.99
Total vegetables, 5-a-Day method					Not applicable
<7	99	81	1.00 (referent)	1.00 (referent)	
7–13.9	252	253	0.82 (0.58–1.15)	0.68 (0.46–1.00)	
14–20.9	189	165	0.94 (0.65–1.34)	0.76 (0.50–1.16)	
⩾21	88	103	0.70 (0.46–1.05)	0.52 (0.31–0.84)	
P for trend‡			.27	.05	
Total vegetables, simple summation					Not applicable
<14	198	167	1.00 (referent)	1.00 (referent)	
14–20.9	150	155	0.82 (0.60–1.11)	0.75 (0.53–1.05)	
21–27.9	115	109	0.89 (0.64–1.24)	0.83 (0.56–1.21)	
⩾28	165	171	0.81 (0.60–1.10)	0.65 (0.45–0.94)	
P for trend‡			.15	.01	
Cruciferous vegetables					
<1	209	172	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–2.9	269	245	0.90 (0.69–1.18)	0.81 (0.60–1.10)	0.84 (0.61–1.14)
⩾3	150	185	0.67 (0.50–0.90)	0.54 (0.38–0.76)	0.59 (0.39–0.90)
P for trend			.01	.01	.02
Green leafy vegetables					
<1	537	503	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–2.9	71	78	0.88 (0.62–1.24)	0.68 (0.46–1.00)	0.75 (0.50–1.11)
⩾3	20	21	0.94 (0.50–1.78)	0.83 (0.40–1.71)	1.06 (0.49–2.26)
P for trend			.40	.10	.41
Carrots					
<1	303	277	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–2.9	233	217	1.00 (0.78–1.28)	0.86 (0.65–1.14)	0.93 (0.69–1.26)
⩾3	92	108	0.76 (0.55–1.06)	0.66 (0.45–0.96)	0.80 (0.52–1.24)
P for trend			.19	.03	.35
Beans					
<1	445	412	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–2.9	151	150	0.93 (0.72–1.21)	0.96 (0.71–1.29)	1.05 (0.77–1.43)
⩾3	32	40	0.74 (0.45–1.19)	0.69 (0.39–1.19)	0.86 (0.48–1.54)
P for trend			.24	.27	.88
Cooked tomatoes					
<1	342	309	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–2.9	222	214	0.94 (0.74–1.20)	0.89 (0.68–1.17)	0.97 (0.73–1.30)
⩾3	64	79	0.73 (0.51–1.05)	0.73 (0.48–1.10)	0.90 (0.57–1.42)
P for trend			.12	.13	.68

(Table continues)

Table 3 (continued). Odds ratios of prostate cancer associated with servings of fruits and vegetables

Servings per week	No. of participants		Odds ratio (95% confidence interval)		
	Case	Control	Unadjusted	Adjusted for covariates*	Adjusted for covariates* + total fruits or vegetables†
Raw tomatoes					
<1	241	242	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–2.9	241	209	1.16 (0.90–1.50)	1.07 (0.80–1.43)	1.20 (0.89–1.62)
⩾3	146	151	0.97 (0.73–1.30)	0.93 (0.67–1.30)	1.22 (0.83–1.80)
P for trend			.99	.76	.26
Other vegetables					
<7	126	100	1.00 (referent)	1.00 (referent)	1.00 (referent)
7–13.9	234	241	0.77 (0.56–1.06)	0.66 (0.46–0.95)	0.81 (0.54–1.21)
14–20.9	172	165	0.83 (0.59–1.16)	0.79 (0.53–1.17)	1.22 (0.70–2.11)
⩾21	96	96	079 (0.54–1.17)	0.56 (0.35–0.91)	1.19 (0.53–2.66)
P for trend			.38	.10	.38

*Fat, energy, race, age, family history of prostate cancer, body mass index, prostate-specific antigen tests in previous 5 years, and education.

†Total servings of fruit or total servings of vegetables calculated by simple summation.

‡Two-sided *P* value of test for trend determined by modeling category of intake as an ordinal variable in a logistic regression model.

complicates epidemiologic studies of prostate cancer risk. For example, in this study, 71% of case participants but only 33% of control participants had received PSA screening in the 5 years before their diagnosis or reference date. Many men who are now diagnosed with prostate cancer may have gone undiagnosed before PSA screening became common. It is possible that risk factors for PSA-detected, early-stage disease could differ from those for clinically manifest tumors. However, in our analyses that were restricted to case participants with aggressive tumors (which would have been diagnosed eventually even without PSA testing), no marked differences from the overall results appeared.

An additional concern is that control participants without PSA screening may have had undiagnosed, latent disease. We found that excluding control participants who had never had a PSA test modestly increased the strength of associations of total vegetable and cruciferous vegetable consumptions with prostate cancer risk, but the associations were not statistically significantly different from the results that included all control participants. Finally, PSA screening is associated with healthful behavior, including higher fruit and vegetable intakes, both in population-based studies in Washington state *(48)* and in the control group in this study. As one might expect, statistical control for number of PSA tests modestly increased the strength of associations between vegetable consumption and prostate cancer risk, similar to the analyses that restricted control participants to those who had received at least some PSA screening.

Three aspects of this study distinguish

Table 4. Odds ratios of prostate cancer associated with nutrient intake

Nutrients per day	No. of participants		Unadjusted odds ratio	Adjusted* odds ratio	*P* for trend†
	Case	Control			
Total carotenoids, μg					.24
<8900	157	156	1.00 (referent)	1.00 (referent)	
8900–11 999	156	138	1.12 (0.82–1.55)	1.13 (0.79–1.63)	
12 000–15 999	155	137	1.12 (0.82–1.55)	1.03 (0.70–1.51)	
⩾16 000	160	171	0.93 (0.68–1.27)	0.81 (0.55–1.21)	
Total carotenoids except lycopene, μg					.16
<3600	190	170	1.00 (referent)	1.00 (referent)	
3600–4899	113	120	0.84 (0.61–1.17)	0.81 (0.56–1.17)	
4900–7299	193	169	1.02 (0.76–1.37)	0.89 (0.63–1.26)	
⩾7300	132	143	0.83 (0.60–1.13)	0.72 (0.48–1.06)	
α-Carotene, μg					.16
<330	164	136	1.00 (referent)	1.00 (referent)	
330–549	159	169	0.78 (0.57–1.07)	0.78 (0.55–1.07)	
550–809	153	152	0.84 (0.61–1.15)	0.78 (0.54–1.12)	
⩾810	152	145	0.87 (0.63–1.20)	0.75 (0.51–1.09)	
β-Carotene, μg					.13
<2200	184	154	1.00 (referent)	1.00 (referent)	
2200–2899	117	133	0.74 (0.53–1.02)	0.73 (0.50–1.06)	
2900–4399	187	173	0.91 (0.67–1.22)	0.77 (0.54–1.09)	
⩾4400	140	142	0.83 (0.60–1.13)	0.72 (0.49–1.07)	
β-Cryptoxanthin, μg					.95
<10	153	149	1.00 (referent)	1.00 (referent)	
10–24	159	160	0.97 (0.71–1.33)	0.95 (0.67–1.35)	
25–44	177	141	1.22 (0.89–1.68)	1.18 (0.82–1.68)	
⩾45	139	152	0.89 (0.65–1.23)	0.93 (0.64–1.36)	
Lutein + zeaxanthin, μg					.09
<800	149	140	1.00 (referent)	1.00 (referent)	
800–1299	184	176	0.98 (0.72–1.34)	0.93 (0.66–1.32)	
1300–1999	169	143	1.11 (0.81–1.53)	0.99 (0.69–1.43)	
⩾2000	126	143	0.83 (0.59–1.15)	0.68 (0.45–1.00)	
Lycopene, μg					.96
<4900	161	163	1.00 (referent)	1.00 (referent)	
4900–6599	122	131	0.94 (0.68–1.31)	0.93 (0.64–1.35)	
6600–9899	207	157	1.34 (0.99–1.80)	1.23 (0.86–1.76)	
⩾9900	138	151	0.93 (0.67–1.27)	0.89 (0.60–1.31)	
Vitamin C, mg					.13
<70	167	141	1.00 (referent)	1.00 (referent)	
70–104	170	173	0.83 (0.61–1.13)	0.86 (0.61–1.23)	
105–149	138	135	0.86 (0.62–1.20)	0.78 (0.53–1.15)	
⩾150	153	153	0.84 (0.62–1.16)	0.75 (0.50–1.11)	

*Controlled for fat, energy, race, age, family history of prostate cancer, body mass index, prostate-specific antigen tests in previous 5 years, and education.

†Two-sided *P* value of test for trend determined by modeling category of intake as an ordinal variable in a logistic regression model.

it from earlier reports on diet and prostate cancer risk. We used a comprehensive FFQ and a nutrient database in which carotenoid values are based on analytic and not imputed values *(27)*. Our statistical models allowed us to analyze effects of individual vegetable groups while controlling for total vegetable consumption. We were, therefore, able to identify a specific protective effect of cruciferous vegetables over and above the protective effect for total vegetable intake.

Our study also differed from others in overall design: We examined dietary risk factors in an age group at low risk for prostate cancer. The incidence of prostate cancer in men under 65 years of age is about 250 per 100 000 compared with 1000 per 100 000 for men 65 years old or older *(49)*. It is possible that cancer in low-incidence age groups is due primarily to inherited susceptibility genes. However, such genes are thought to explain less than 30% of cancers diagnosed in men less than 65 years of age *(50)*, and additional studies of risk factors in low-incidence groups may allow more clear identification of environmental exposures related to risk.

We found protective effects of vegetables, particularly cruciferous vegetables, on prostate cancer risk. This study provides justification for further research to differentiate the effects of specific vegetables and to discover the mechanisms underlying associations between total and cruciferous vegetables and risk of prostate cancer. It also provides support for the general public health recommendation to increase vegetable intake.

REFERENCES

(1) World Cancer Research Fund. Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 1997.

(2) Ohno Y, Yoshida O, Oishi K, Okada K, Yamabe H, Schroeder FH. Dietary beta-carotene and cancer of the prostate: a case–control study in Kyoto, Japan. Cancer Res 1988;48:1331–6.

(3) Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Res 1989;49:1857–60.

(4) Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, et al. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. Cancer Res 1990;6836–40.

(5) La Vecchia C, Negri E, D'Avanzo B, Frahceshci S, Boyle P. Dairy products and the risk of prostatic cancer. Oncology 1991;8:406–10.

(6) Le Merchand L, Hankin JH, Kiolonel LN, Wilkens LR. Vegetable and fruit consumption in relation to prostate cancer risk in Hawaii: a reevaluation of the effect of dietary beta-carotene. Am J Epidemiol 1991;33:215–9.

(7) Talamini R, Franceschi S, La Vecchia C, Serraino D, Barra S, Negri E. Diet and prostatic cancer: a case control study in Northern Italy. Nutr Cancer 1992;18:227–86.

(8) Lee MM, Wang RT, Hsing AW, Gu FL, Wang T, Spitz M. Case–control study of diet and prostate cancer in China. Cancer Causes Control 1998;9:545–52.

(9) Tzonou A, Signorello L, Lagiou P, Wuu J, Trichopoulos D, Trichopoulos A. Diet and cancer of the prostate: a case–control study in Greece. Int J Cancer 1990;80:704–8.

(10) Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 1995;87: 1767–76.

(11) Hirayama T. Epidemiology of prostate cancer with special reference to the role of diet. Natl Cancer Inst Monogr 1979;53:149–55.

(12) Schuman L, Mandel J, Radke A. Some selected features of the epidemiology of prostatic cancer: Minneapolis–St Paul, Minnesota case–control study, 1976–1979. In: Magnus K, editor. Trends in cancer incidence: causes and implications. Washington (DC): Hemisphere Publishing Corporation; 1982. p. 345–54.

(13) Graham S, Haughey B, Marshall J, Priore R, Buers T, Rzepka T, et al. Diet in epidemiology of carcinoma of the prostate gland. J Natl Cancer Inst 1983;70:687–92.

(14) Snowdon DA, Phillips RL, Choi W. Diet, obesity, and risk of fatal prostate cancer. Am J Epidemiol 1984;120:244–50.

(15) Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological Study of prostatic cancer by matched-pair analysis. Prostate 1985;6:423–36.

(16) Ross RK, Shimizu H, Paganini-Hill A, Honda G, Henderson BE. Case–control studies of prostate cancer in blacks and whites in southern California. J Natl Cancer Inst 1987;78: 869–74.

(17) Mills PK, Beeson WL, Phillips RL, Fraser GE. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. Cancer 1989;64: 598–604.

(18) Walker ARP, Walker BF, Tsotetsi NG, Sebitso C, Siwedi D, Walker AJ. Case–control study of prostate cancer in black patients in Soweto, South Africa. Br J Cancer 1992;65:438–41.

(19) Key T, Silcocks P, Devey G, Appleby P, Bishop D. A case–control study of diet and prostate cancer. Br J Cancer 1997;76:678–87.

(20) Schuurman AG, Goldbohm RA, Dormant E, van den Brandt PA. Vegetable and fruit consumption and prostate cancer risk: a cohort study in The Netherlands. Cancer Epidemiol Biomark Prev 1998;7:673–80.

(21) Humphrey PA, Walther PJ. Adenocarcinoma of the prostate. Am J Clin Pathol 1993;100: 256–69.

(22) Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974;111:58–64.

(23) Campbell MK, Reynolds KD, Havas S, Curry S, Bishop D, Nicklas T, et al. Stages of change for increasing fruit and vegetable consumption among adults and young adults participating in the National 5-A-Day for Better Health Community Studies. Health Educ Behav 1999;6: 513–34.

(24) Krebs-Smith SM, Heimendinger J, Subar AF, Patterson BH, Pivonka E. Using food frequency questionnaires to estimate fruit and vegetable intake: association between the number of questions and total intakes. J Nutr Edu 1995;27:80–5.

(25) Kristal AR, Shattuck AL, Williams AE. Food frequency questionnaires for diet intervention research. Proceedings of the 17th National Nutrient Databank Conference; 1994.

(26) Nutrition Coordinating Center: Nutrition Data System. Minneapolis (MN): University of Minnesota. Version 2; 1998. p. 92.

(27) Agricultural Research Service: USDA Nutrient Database for Standard Reference. Washington (DC): U.S. Department of Agriculture; 1998.

(28) Kristal AR, Feng Z, Coates RJ, Oberman A, George V. Associations of race/ethnicity, education, and dietary intervention with the validity and reliability of a food frequency questionnaire: the Women's Health Trial Feasibility Study in Minority Populations. Am J Epidemiol 1997;146:856–69.

(29) Campbell D, Gross M, Martini M, Grandits G, Slavin J, Potter J. Plasma carotenoids as biomarkers of vegetable and fruit intake. Cancer Epidemiol Biomark Prev 1994;3:493–500.

(30) Breslow NE, Day NE. Statistical methods in cancer research. Vol II. The design and analysis of cohort studies. Lyon (France): IARC; 1987.

(31) Wacholder S, Schatzkin A, Freedman L, Kipnis V, Hartman A, Brown C. Can energy adjustment separate the effects of energy from those of specific macronutrients. Am J Epidemiol 1994;140:848–55.

(32) Tucker K, Chen H, Vogel S, Wilson P, Schaefer E, Lammi-Keefe C. Carotenoid intakes, assessed by dietary questionnaire, are associated with plasma carotenoid concentrations in an elderly population. J Nutr 1998;129:438–45.

(33) Moskaluk C, Duray P, Cowan K, Linehan M, Merino M. Immunohistochemical expression of pi-class glutathione *S*-transferase is downregulated in adenocarcinoma of the prostate. Cancer 1997;79:1595–9.

(34) Lee W, Morton R, Epstein J, Brooks J, Campbell P, Bova G, et al. Cytidine methylation of regulatory sequences near the pi-class glutathione *S*-transferase gene accompanies human prostatic carcinogenesis. Proc Natl Acad Sci U S A 1994;91:11733–7.

(35) Zhang Y, Talalay P, Cho C, Posner G. A major inducer of anticarcinogenic protective enzymes from broccoli: isolation and elucidation of structure. Proc Natl Acad Sci U S A 1992;89: 2399–403.

(36) Prochaska H, Sanatamaria A, Talalay P. Rapid detection of inducers of enzymes that protect against carcinogens. Proc Natl Acad Sci U S A 1992;89:2394–8.

(37) Beecher C. Cancer preventive properties of varieties of Brassica Oleaceae: a review. Am J Clin Nutr 1994;59:1166S–70S.

(38) Verhagen H, Poulsen H, Loft S, van Popple G, Willems M, Bladeren P. Reduction of oxidative DNA-damage in humans by Brussels sprouts. Carcinogenesis 1995;16:969–70.
(39) Verhoeven DT, Goldbohm RA, Van Poppel G, Verhagen H, Van den Brandt PA. Epidemiological studies on Brassica vegetables and cancer risk. Cancer Epidemiol Biomark Prev 1996;5:733–48.
(40) Verhagen H, de Vries A, Njhoff W, Schouten A, van Poppel G, Peters W, et al. Effect of Brussels sprouts on oxidative DNA-damage in man. Cancer Lett 1997;114:127–30.
(41) Giovannucci E, Clinton S. Tomatoes, lycopene, and prostate cancer. Proc Soc Exp Biol Med 1998;218:129–39.
(42) Gann P, Ma J, Giovannucci E, Willett W, Sacks F, Hennekens C, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res 1999;59:1225–30.
(43) Kristal A, Cohen J. Tomatoes, lycopene and prostate cancer. How strong is the evidence? Am J Epidemiol 2000;151.
(44) Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. J Natl Cancer Inst 1999; 91:317–31.
(45) Meyer F, Bairati I, Fradet Y, Moore L. Dietary energy and nutrients in relation to preclinical prostate cancer. Nutr Cancer 1997;29: 120–6.
(46) Nomura AM, Stemmermann GN, Lee J, Craft N. Serum micronutrients and prostate cancer in Japanese Americans in Hawaii. Cancer Epidemiol Biomark Prev 1997;6:487–91.
(47) Friedenriech C, Slimani N, Riboli E. Measurement of past diet: review of previous and proposed methods. Epidemiol Rev 1992;14: 177–96.
(48) Close D, Kristal A, Patterson R, White E. Associations of demographic and health-related characteristics with prostate cancer screening in Washington State. Cancer Epidemiol Biomark Prev 1998;7:627–30.
(49) Stanford JL, Stephenson RA, Coyle LM. Prostate cancer trends 1973–1995, SEER Program. Washington (DC): U.S. Govt Print Off; 1999.
(50) Carter BS, Bova GS, Beaty TH, Steinberg GD, Childs B, Issacs WB, et al. Hereditary prostate cancer: epidemiologic and clinical features. J Urol 1993;150:797–802.

NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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