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Fruit and Vegetable Intake and Incidence of Bladder Cancer in a Male Prospective Cohort

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Background: Previous epidemiologic studies of fruit and vegetable intake and bladder cancer risk have yielded inconsistent results, especially with regard to the types of fruits and vegetables consumed. We examined total fruit and vegetable intake, as well as intakes of subtypes of fruits and vegetables, in relation to bladder cancer risk in a large male prospective cohort study. Methods: Two hundred fifty-two cases of incident bladder cancer were diagnosed from 1986 through January 31,1996, among 47 909 men enrolled in the Health Professionals Follow-up Study. Each participant in this cohort completed a 131-item food-frequency questionnaire in 1986 and subsequently in 1990 and 1994. We used logistic regression analyses to examine fruit and vegetable intake in relation to bladder cancer risk, after adjusting for age, history of cigarette smoking, current smoking status, geographic region, total fluid intake, and caloric intake. Results: We observed a weak, inverse association that was not statistically significant between total fruit and vegetable intake and bladder cancer risk. Intake of cruciferous vegetables was inversely associated with risk (relative risk = 0.49; 95% confidence interval = 0.32–0.75, for the highest category of cruciferous vegetable intake compared with the lowest), but intakes of yellow or green leafy vegetables or carotenoid-rich vegetables were not associated with risk. Individual cruciferous vegetables, except for coleslaw, were all inversely related to bladder cancer risk, but only the associations for broccoli and cabbage were statistically significant. *Conclusions:* Data from this study indicate that high cruciferous vegetable consumption may reduce bladder cancer risk, but other vegetables and fruits may not confer appreciable benefits against this cancer. [J Natl Cancer Inst 1999;91:605–13]

Bladder cancer is the sixth most commonly diagnosed cancer in the United States. In 1997, approximately 39500 men and 15 000 women were estimated to be newly diagnosed with bladder cancer *(1)*. The majority (73%) of bladder cancers are detected at an early stage, and patients with such cancers have a 5-year survival rate of 92% *(1)*. However, for patients with superficial cancers that typically recur, the psychological burden and costs to the health care system of repeated diagnostic evaluations and therapy are substantial.

Tobacco smoking is the most clearly established modifiable risk for bladder cancer, but dietary fruits and vegetables, as for many other cancers, may play a preventative role ***(2)***. In addition to being a rich source of certain vitamins, minerals, and fiber, these foods are a source of thousands of phytochemicals that may have anticancer properties (3). Proposed mechanisms for the antitumor activity of these phytochemicals are numerous; they include antioxidant properties *(4)*, activation of carcinogen-detoxifying enzymes *(5)*, and inhibition of growth factor stimulation of the tumor cell proliferation ***(6)***.

Overall, epidemiologic studies on bladder cancer incidence support a protective effect of fruit and vegetable intake *(7–13)*, although some studies have reported no association *(14–17)*. Previous studies also have been inconsistent with regard to which fruits and vegetables or which subtype of vegetables (e.g., yellow versus green leafy vegetables) may be responsible for an inverse association with bladder cancer. Consequently, it is difficult to determine if the observed relationships represent a cumulative influence of many chemopreventive agents obtained from total fruit and vegetable intake or a more specific effect of a few anticarcinogenic agents obtained from a subset of fruits or vegetables. Whether the putative beneficial effects of fruits or vegetables is modified by cigarette smoking **status** is also poorly understood.

The purpose of this study was to examine prospectively the relationship between total and type of fruit and vegetable intake and bladder cancer risk in males.

SUBJECTS AND METHODS

Study Population

The Health Professionals Follow-up Study is a prospective cohort study initiated in 1986, when 51 529 predominantly white men aged 40–75 years answered a detailed questionnaire by mail on diet and medical history. This cohort consists of dentists (57.6%). veterinarians (19.6%), pharmacists (8.1%), optometrists (7.3%). osteopathic physicians (4.3%), and podiatrists (3.1%). All 50 states of the United States were represented, and no exclusions were made by race. Every **2** years, follow-up questionnaires were mailed to all surviving cohort members, up to six times per follow-up cycle for nonrespondents, to update data on medical conditions and exposures. This investigation **was** approved by **the** Human Subjects Committee of the Harvard School of Public Health.

To form the cohort for analysis, we excluded 1596 men with implausibly high or **low** scores for total food intake (outside the range of 800–4200 kcal/day) or with 70 items or more left blank on the baseline dietary questionnaire and 18

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men with missing date of birth. In addition, 2006 men with cancers (excluding nonmelanoma skin cancer) diagnosed before 1986 were excluded because these men may have changed their diets as a result of their disease. The remaining 47909 men were eligible for follow-up. The follow-up rate for this cohort averaged 94% per follow-up cycle during the five biennial cycles during the period from 1986 through 1996. The National Death Index was used to determine vital status for nonrespondents, and the remaining nonrespondents were assumed to be alive and at risk for bladder cancer.

Dietary Assessment

To assess dietary intake, we used a 131-item semiquantitative food-frequency questionnaire (FFQ)*(18)*, which is an expanded version of a previously validated questionnaire (19). The baseline dietary questionnaire was administered in 1986, and dietary intake information was updated in 1990 and 1994. The questionnaire assesses average frequency of intake over the previous year. For each man, we calculated caloric and nutrient intakes by multiplying the frequency that each food item was reported by the caloric or nutrient content for the specified portion size. Food composition data were primarily based on the nutrient database of the U.S. Department of Agriculture *(20)*. For carotenoid values, we used the new U.S. Department of Agriculture–National Cancer Institute database that was developed for fruits and vegetables and that includes data from a publication on tomato-based food products *(21,22)*.

For the examination of food groups, such as total intake of fruits and vegetables, frequency of consumption was summed across all foods belonging to each group. Because most servings for fruits and vegetables specified on the FFQs are similar in size (e.g., one-half cup or one fruit), we did not standardize intake before summing up frequency of use. The "total vegetable" group consists of the following: string beans; broccoli; sauerkraut; coleslaw and uncooked cabbage; cooked cabbage; cauliflower; Brussels sprouts; carrots; corn; peas or lima beans; mixed vegetables; beans or lentils (baked or dried); alfalfa sprouts; celery; mushrooms (fresh, cooked, or canned); yellow (winter) squash; eggplant, zucchini, or other summer squash; yams or sweet potatoes; spinach (cooked); spinach (raw); kale and mustard or chard greens; iceberg or head lettuce; romaine or leaf lettuce; green pepper; garlic (fresh or powdered); tomatoes; tomato juice; tomato sauce; red chili sauce; and tofu or soybeans. The "total fruit" group consists of the following: raisins; avocado; bananas; cantaloupe; Watermelon; fresh apples or pears; apple juice or cider; oranges; orange juice; grapefruit; grapefruit juice; other fruit juices; strawberries; blueberries; and peaches, apricots, or plums.

Fruits and vegetables were also grouped into the following categories: yellow vegetables, consisting of carrots, yams, sweet potatoes, and yellow squash; green leafy vegetables, consisting of spinach (raw and cooked), kale (mustard and chard greens), and romaine and leaf lettuce; cruciferous vegetables ***(Brassica oleracea*** family), consisting of broccoli, cabbage, cauliflower, Brussels sprouts, coleslaw, sauerkraut, and kale (note that the "kale" item on the questionnaire also includes mustard and chard greens that do not belong to the cruciferous *B. **oleracea*** family); and citrus fruits, consisting of oranges, orange juice, grapefruit, and grapefruit juice. Similar groupings have been reported previously in epidemiologic studies *(17,23)* examining associations between fruit and vegetable intakes and cancer outcomes and represent, to some extent, foods rich in certain phytochemicals that may influence cancer risk (i.e., yellow vegetables are high in β-carotene, green leafy vegetables are high in lutein, cruciferous vegetables are high in glucosinolates. and citrus fruits are high in vitamin C).

A reproducibility and validity study of the FFQ among 127 men in this cohort indicated that most foods are reported reasonably well: Pearson correlations between the average intake assessed by two I-week diet records completed 6 months apart and I-FFQ (completed after the diet records) ranged from 0.25 to 0.95 for specific fruits and vegetables, and the median correlations for fruits and vegetables were .77 and .46, respectively *(24)*. Correlations between the two diet records and the 1-FFQ for fruit and vegetable groupings used in this study were calculated by use of data from the validation study and were as follows: .37 for cruciferous vegetables, .40 for vegetables and yellow vegetables. .45 for green leafy vegetables, .61 for total fruits and vegetables, .78 for fruits. and .87 for citrus fruits. Intakes of carotenoids (a-carotene. p-carotene. lutein. lycopene. and β-cryptoxanthin) were reported previously to correlate reasonably well with specific carotenoid plasma levels in a subset of men from this cohort (correlations ranged between .35 and .47) *(25)*.

Assessment of Nondietary Factors

At baseline and biennially thereafter, men provided information on their state of residence. current cigarette smoking status. exercise habits. weight. height. and medication use. The baseline questionnaire provided detailed information on past smoking habits, time since quitting. and average number of cigarettes smoked per day before age 15 and at ages 15–19 years, 20–29 years. 30–39 years. 40–49 years. 50–59 years, and 60 years and older. To control for smoking, total pack-years of smoking was derived to incorporate all past smoking experience. One cigarette pack-year is equivalent to having smoked one pack or 20 cigarettes per day for an entire year.

Case Ascertainment

On each questionnaire, participants indicated whether they had been diagnosed with any major cancer (e.g., prostate or colon cancer), heart disease, or other medical conditions. Participants were required to write in "bladder" in a space provided for "other cancers." We confirmed the self-reported diagnosis of bladder cancer by reviewing medical records. When denied permission to obtain medical records. we attempted to confirm the initial cancer report and date of diagnosis with an additional letter or telephone call. If the primary cause of death, reported by the National Death Index, was a previously unreported bladder cancer. we contacted family members to obtain permission to retrieve medical records or, at the very least, to confirm the diagnosis of bladder cancer. For three bladder cancer cases, we used death certificates to confirm a previous. unconfirmed self-reported diagnosis of bladder cancer.

The end points in this study were 252 bladder cancer cases newly diagnosed during the period from 1986 through January 31, 1996. of which 213 were confirmed with medical records. Unconfirmed cases were kept in the analyses after verifying that similar results were obtained when those cases were excluded. On the basis of review of pathology reports, more than 90% of bladder cancer cases were transitional cell carcinomas.

Statistical Analysis

We computed person-time of follow-up for each participant from the return date of the 1986 questionnaire to the date of bladder cancer diagnosis, to the day of death from any cause, or January 31, 1996, whichever came first. In the main analysis, exposure categories were determined by the 1986 questionnaire (except for age and current smoking status, which were updated every 2 years in all analyses). The incidence rate for each category of fruit and vegetable intake was calculated as the number of cases with bladder cancer divided by the person-time of follow-up. Cut points for the different groupings of fruit and/or vegetable intakes were obtained by dividing each into five even categories (i.e., quintiles) and then finding the closest whole (or half) frequency of use for each cutoff. By doing this, we created categories of intake that can be easily interpreted. To adjust for age (5-year categories), pack-years of smoking, and current smoking status (updated every 2 years), we used pooled logistic regression ***(26)***. This approach is asymptotically equivalent to the Cox regression model with time-dependent covariates, given short time intervals and low probability of the outcome within the interval ***(26)***. In multivariate (MV) analyses, in addition to age and pack-years of smoking, we adjusted for geographic region and fluid intake because both of these variables were risk factors in this population. U.S. states were grouped into five geographic regions, according to the U.S. Census definitions: West, Midwest, South, Northeast, and Pacific. Total caloric intake was also included in MV models to minimize extraneous variation introduced by underreporting or overreporting in the FFQ (27). Because this cohort consists of health professionals, the socioeconomic status of the study members is sufficiently homogeneous not to have to control for this variable.

In a separate analysis, we examined the relationship between total and type of fruit and vegetable intakes and bladder cancer incidence by updating the baseline food groups with diet from subsequent questionnaires (in 1990 and 1994). In these analyses, dietary data from the 1986 questionnaire were used to predict outcomes during the period from 1986 to 1990. the average of 1986 and 1990 dietary intakes was used to predict outcomes during the period from 1990 to 1994. and the average of 1986. 1990. and 1994 was used for subsequent cases (i.e., 1994 to 1996). Cumulative averaging may reduce within-person variation and better represent long-term intake. Tests for trend were obtained by assigning the median value for each category and modeling this variable as a continuous variable. using pooled logistic regression for MV analyses. Tests for statistical (multiplicative) interaction were performed by use of likelihood ratio tests.

RESULTS

As expected, smoking was strongly associated with the risk of bladder cancer. and the incidence of this cancer increased

with age in this cohort. Men with a history of heavy cigarette smoking had a substantially higher risk of bladder cancer (relative risk [RR] = 3.6; 95% confidence interval [CI] = 2.2–4.6 for 65 or more pack-years of smoking cigarettes compared with never smokers).

Total fruit and vegetable intake was not significantly associated with the risk of bladder cancer after adjustment was made for pack-years of smoking, current smoking status, age, geographic region in the United States, and total fluid and caloric intake (two-sided P value, test for trend = .25; Table 1). The MV RR of bladder cancer incidence for the top category of total fruit and vegetable intake (>8.0 servings/day), compared with the bottom category (<3.5 servings/day) was 0.75 (95% CI = 0.49–1.14). Although the age-adjusted association between total fruit and vegetable intake and bladder cancer risk was significant before adjustment for other variables (P for trend = .04), pack-years of smoking was inversely associated with fruit and vegetable consumption and accounted for all the differences between the age-adjusted and the MV analyses. Thus, when we included only age, pack-years of smoking, current smoking status, and total fruit and vegetables in a separate model, the RR for the highest quintile of total fruit and vegetable intake compared

Table 1. Relative risks (RRs) and 95% confidence intervals (95% CIs) for incident bladder cancer by categories of total fruit and vegetables, fruit, vegetables, or other groupings of vegetable intake*

	Categories of intake					Two-sided
	1	2	3	4	5	*P* for trend
Fruits and vegetables, servings/day†	<3.5	3.5–4.5	4.6–6.0	6.1–8.0	>8.0	
Median	2.7	4.0	5.2	6.9	9.9	
No. of cases	59	38	55	53	47	
Person-years	91 912	68 894	96 795	90 474	87 381	
RR	1.0	0.76	0.74	0.73	0.64	.04
MV RR (95% CI)	1.0 (referent)	0.80 (0.53–1.21)	0.82 (0.56–1.20)	0.82 (0.56–1.22)	0.75 (0.49–1.14)	.25
Fruits, servings/day	≤1.0	1.1–1.5	1.6–2.5	2.6–3.5	>3.5	
Median	0.6	1.3	2.0	2.9	4.5	
No. of cases	36	53	66	50	47	
Person-years	78 080	64417	129469	84 775	78 714	
RR	1.0	1.55	0.84	0.88	0.86	.09
MV RR (95% CI)	1.0 (referent)	1.69 (1.10–2.59)	0.98 (0.65–1.49)	1.10 (0.70–1.71)	1.12 (0.70–1.78)	.68
Vegetables, servings/day	<2.0	2.0–2.9	3.0–3.9	4.0–4.9	≥5.0	
Median	1.5	2.5	3.5	4.4	6.3	
No. of cases	63	73	38	38	40	
Person-years	97 073	108 293	87 554	60 156	82 379	
RR	1.0	1.02	0.64	0.91	0.68	.03
MV RR (95% CI)	1.0 (referent)	1.04 (0.74–1.47)	0.67 (0.44–1.01)	0.96 (0.63–1.45)	0.72 (0.47–1.09)	.09
Cruciferous vegetables, servings/wk‡	≤1.0	1.1–2.0	2.1–3.0	3.1–4.9	≥5.0	
Median	0.5	1.8	2.5	3.9	7.0	
No. of cases	65	49	45	60	33	
Person-years	82 689	99 500	80 140	89 081	84 045	
RR	1.0	0.65	0.72	0.84	0.45	.002
MV RR (95% CI)	1.0 (referent)	0.68 (0.47–0.98)	0.74 (0.51–1.09)	0.88 (0.62–1.26)	0.49 (0.32–0.75)	.008
Yellow vegetables, servings/unit time§	≤1–2/mo	0.5–1/wk	1–2/wk	2–3/wk	>3/wk	
Median (servings/wk)	0.5	0.9	1.5	3.0	6.0	
No. of cases	51	62	58	42	39	
Person-years	94 768	91 283	101 272	85 543	62 588	
RR	1.0	1.20	0.94	0.74	0.87	.14
MV RR (95% CI)	1.0 (referent)	1.25 (0.86–1.81)	1.01 (0.69–1.48)	0.84 (0.55–1.27)	1.01 (0.66–1.56)	.50
Green leafy vegetables, servings/unit time‖		1–2/mo	1–2/wk	2–3/wk	>3/wk	
Median (servings/wk)	0	0.5	1.4	3.0	6.4	
No. of cases	43	45	85	43	36	
Person-years	71 171	71 574	148293	76 954	67 463	
RR	1.0	1.09	1.09	1.02	0.98	.70
MV RR (95% CI)	1.0 (referent)	1.06 (0.70–1.61)	1.08 (0.75–1.56)	1.02 (0.67–1.57)	0.99 (0.63–1.56)	.81

*RRs are adjusted for age; multivariate RRs (MV RRs) are adjusted for age, pack-years of cigarette smoking (i.e., number of packs smoked per day x number of years of smoking), current smoking status, geographic region, total fluid intake, and caloric intake.

†Vegetables = string beans; broccoli; sauerkraut; coleslaw and uncooked cabbage; cooked cabbage; cauliflower; Brussels sprouts; carrots; corn; peas or lima beans; mixed vegetables; beans or lentils (baked or dried); alfalfa sprouts; celery; mushrooms (fresh, cooked, or canned); yellow (winter) squash; eggplant; zucchini; other summer squash; yams or sweet potatoes; spinach (cooked); spinach (raw); kale (mustard or chard greens); iceberg or head lettuce; romaine or leaf lettuce; green pepper; garlic (fresh or powered); tomatoes; tomato juice; tomato sauce; red chili sauce; and tofu or soybeans. Fruits = raisins; avocados; bananas; cantaloupe; watermelon; fresh apples or pears; apple juice or cider; oranges; orange juice; grapefruit; grapefruit juice; other fruit juice; strawberries; blueberries; and peaches, apricots, or plums.

‡Cruciferous vegetables = cabbage, cauliflower, Brussels sprouts, kale, sauerkraut, coleslaw, and broccoli.

§Yellow vegetables = yellow squash, yams, sweet potatoes, and carrots.

‖Green leafy vegetables = spinach (raw and cooked), kale (mustard and chard greens), and romaine and leaf lettuce.

with the lowest was identical to that from the full MV model (RR = 0.75; 95% CI = 0.51–1.10).

We then examined intake of fruits and vegetables separately and further divided vegetables into preassigned groupings (yellow, green leafy, and cruciferous vegetables). The relationship between total fruit (including fruit juices) intake and bladder cancer risk was null after we controlled for potential confounders. Similarly, citrus fruits were not associated with bladder cancer risk (MV RR = 1.02; 95% CI = 0.65–1.60, for comparison between the top and the bottom categories). The association between total vegetable intake and bladder cancer risk was inverse; however, in the MV analysis, the association was not statistically significant (*P* for trend = .09). **A** high intake of yellow vegetables was not associated with a reduced risk of bladder cancer, and no significant association was observed for intake of green leafy vegetables.

In an age-adjusted model, we observed a 51% risk reduction of bladder cancer among those consuming a high intake (>5.0 servings/week) compared with a low intake of cruciferous vegetables (≤ 1.0 serving/week; Table 1). The inverse association for cruciferous vegetable intake and bladder cancer risk persisted after adjustment for potential confounders and remained statistically significant (*P* for trend = .008). When we modeled cruciferous vegetables and total vegetables simultaneously using the same categories as those used in Table 1, the highest intake of cruciferous vegetable (≥5.0 servings/week) compared with the lowest (≤ 1.0 serving/week) was statistically significant (MV RR = 0.57; 95% CI = 0.36–0.93), whereas the RR for the top category (>8.0 servings/day) versus the bottom category (<3.5 servings/day) of total vegetable intake was not significant (MV RR = 0.83; 95% CI = 0.52–1.35). On average, cruciferous vegetables account for 14% of total vegetable consumption in this cohort.

In an additional analysis, we divided men according to tertiles of cruciferous vegetable intake and tertiles of total vegetable intake and examined the relationship between cruciferous vegetable intake and bladder cancer risk at different levels of total vegetable intake (Table 2). Compared with low cruciferous and low total vegetable intake, high intake of cruciferous vegetables was associated with a lower risk of bladder cancer in each of the tertiles of total vegetable intake. In contrast, total vegetable intake was not strongly inversely associated with bladder cancer risk in the lower tertiles of cruciferous vegetable intake. The RRs were somewhat attenuated compared with the quintile analysis because the range of intake was narrower in the tertile analysis. The median intake of cruciferous vegetables in the high cruciferous/high total vegetable intake category was 6.5/week compared with 4.4/week for the high cruciferous/low vegetable intake category, probably explaining the slight inverse trend across the tertiles of total vegetable intake in the top cruciferous vegetable tertile. Therefore. the inverse association observed between cruciferous vegetable intake and bladder cancer risk is independent of an increase in total vegetables and may be explained by one or more phytochemical(s) specific to those vegetables.

In this cohort of men, broccoli was the most frequently consumed cruciferous vegetable. Associations between individual cruciferous vegetables and bladder cancer risk are reported in Table 3. Intakes of broccoli, cabbage, cauliflower, Brussels sprouts. and kale were inversely associated with the risk of bladder cancer. but the association for cauliflower, Brussels sprouts,

Table 2. Multivariate relative risks (MV RRs) and 95% confidence intervals (95% CIs) of incident bladder cancer by tertiles of cruciferous vegetable intake and tertiles of total vegetable intake*

	Cruciferous vegetable intake, servings per week		
Total vegetable intake	<1.8	1.8–3.4	>3.4
<2.7 servings/day			
MV RR	1.0†	0.81	0.71
95% CI	—	0.53–1.23	0.34–1.48
No. of bladder cancercases	69	32	8
2.74.2 servings/day			
MV RR	0.82	0.99	0.68
95% CI	0.51–1.32	0.66–1.50	0.42–1.12
No. of bladder cancer cases	23	35	21
>4.2 servings/day			
MV RR	0.95	0.81	0.59
95% CI	0.52–1.73	0.47–1.37	0.38–0.90
No. of bladder cancercases	13	18	33

*MV RRs are adjusted for age, pack-years of cigarette smoking (i.e., number of packs smoked per day x number of years of smoking), current smoking status, geographic region, total fluid intake, and caloric intake.

†Referent category.

and kale intake was not statistically significant. Intakes of sauerkraut and coleslaw were not associated with the risk of bladder cancer.

To examine in more detail the associations between individual cruciferous vegetables and bladder cancer risk, we created joint classifications of broccoli and cabbage intake and broccoli and cauliflower intake (Table 4). Results of broccoli and cabbage cross-tabulations indicate that high intakes of broccoli and cabbage are independently associated with bladder cancer risk, because the MV RRs decreased with increasing intake of broccoli and cabbage, independently of each other. The MV RR of bladder cancer for high intake of both broccoli and cabbage compared with low intake of both was 0.34 (95% CI = 0.12–0.92). In contrast, cauliflower did not appear to be associated with bladder cancer risk once stratified by broccoli intake (Spearman correlation between cauliflower and broccoli = .48). Independent effects of broccoli and cabbage were confirmed in an MV model that included an interactive term for broccoli and cabbage. (Broccoli and cabbage were modeled continuously after assigning the median values to each category; *P* for trend for broccoli = .007, and *P* for trend for cabbage = .02.) The likelihood ratio test did not indicate any significant interaction between these two vegetables.

In Table 5, the association between cruciferous vegetable intake and bladder cancer risk was examined across strata of cigarette smoking status. Cruciferous vegetable intake in this analysis was grouped into four categories because of small numbers of cases. The relationships between cruciferous vegetable intake and bladder cancer risk were inverse in all three groups (never, past, and current smokers), but the relationship was statistically significant only among never smokers (*P* for trend = .005). There was no statistically significant interaction between cruciferous vegetable intake and smoking status.

In an attempt to reduce within-person error and to better measure long-term intake, we examined the association between the cumulative, updated average intake of the different groups

Table 3. Relationship between intake of individual cruciferous vegetable, and bladder cancer Incidence'

Vegetable†	Categories of intake <1/wk	1/wk	≥2/wk	Two-sided *P* for trend
Broccoli				
No. of cases	145	69	38	
Person-years	190552	152385	92519	
RR	1.0	0.69	0.56	.002
MV RK (95% CI)	1.0 (referent)	0.71 (0.53–0.95)	0.61 (0.42–0.87)	.009

Vegetable?	Categories of intake <1/mo	1–3/mo	≥1/wk	Two-sided *P* for trend
Cabbage				
No. of cases	160	77	15	
Person-years	270445	128531	36479	
RR	1.0	0.91	0.56	.04
MV RR (95%CI)	1.0 (referent)	0.91 (0.69–1.20)	0.57 (0.33–0.97)	.05
Cauliflower				
No. of cases	96	91	65	
Person-years	127993	179426	128036	
RR	1.0	0.69	0.72	.04
MV RR (95%CI)	1.0 (referent)	0.73 (0.54-0.97)	0.78 (0.57–1.07)	.11
Brussels sprouts				
No. of cases	143	83	26	
Person-years	253651	128152	53651	
RR	1.0	1.15	0.80	.62
MV RR (95%CI)	1.0 (referent)	1.16(0.88–1.52)	0.83 (0.54–1.26)	.75
Sauerkraut				
No. of cases	188	54	10	
Person-years	322604	96550	16301	
RR	1.0	0.95	0.94	.71
MV RR (95%CI)	1.0(referent)	0.93 (0.68–1.26)	0.92 (0.49–1.75)	.63
Coleslaw				
No. of cases	68	115	69	
Person-years	143329	184649	107477	
RR	1.0	1.28	1.15	.45
MV RR (95%CI)	1.0 (referent)	1.29 (0.95–1.74)	1.20 (0.85–1.69)	.32
Kale				
No. of cases	225	19	8	
Person-years	378712	39708	17034	
RR	1.0	0.81	0.70	.20
MV RR (95%CI)	1.0(referent)	0.79 (0.49–1.27)	0.68 (0.34–1.39)	.18

*Relative risks (RRs) are adjusted for age; multivariate RRs (MV RRs) are adjusted for age, pack-years of cigarette smoking (i.e., number of packs smoked per day × number of years of smoking), current smoking status, geographic region, total fluid intake, and caloric intake. 95% CI = 95% confidence interval.

†Servings = one-half cup.

of fruits and vegetables using the same cut points as those used in the main analyses. Results from these analyses were similar to those in which the baseline questionnaire only was used. For example, the RRs of incident bladder cancer obtained by updating cruciferous vegetables in an MV model were 0.76, 0.78, 0.79, and 0.56 for the second to the fifth highest category compared with the bottom category, respectively.

To obtain a measure of vegetable intake representative of very long term intake, we restricted the analyses to those individuals who reported having had the same vegetable intake "overthe past 10 years" on the 1586 questionnaire. One hundred fifty-four cases were available for these analyses. MV RRs for cruciferous vegetable intake and bladder cancer risk were very similar to those observed in the main analyses (top versus bottom category comparison MV RR = 0.47; 95% CI = 0.25–0.87). In the fruit and vegetable analysis, the association with bladder cancer risk was weaker than in the main analysis (top versus bottom category comparison MV RR = 1.06; 95% CI = 0.62–1.82).

We also examined each 15 individual fruit and 30 vegetable items present on the baseline questionnaire. Excluding cruciferous vegetables, no individual vegetable or fruit item was statistically associated with bladder cancer risk in MV models. In addition, only three of the 30 vegetable items besides broccoli, cabbage, cauliflower, Brussels sprouts, and kale had MV RRs below 0.80 for the top versus the bottom category of intake; these vegetables were cooked spinach, yams, and yellow squash, and associations were not statistically significant.

Because carotenoids are found in various fruits and vegetables, have antioxidant properties, and have been shown to have an anticarcinogenic effect on bladder cancer in experimental studies *(28)*, we examined the relationship between the dietary intake of five major carotenoids and bladder cancer risk. In this study, we observed no association between intake of lutein, lycopene, a-carotene, β-carotene, or β-cryptoxanthin and risk of bladder cancer (Table 6).

Table 4. Multivariate relative risks (MV RRs) and 95% confidence intervals (95% CIs) of incident bladder cancer by categories of cruciferous vegetable intake*

Cabbage. servings/mo	Broccoli, servings/wk <1	1	>1
c2			
MV RR	1.0†	0.67	0.45
95% CI	—	0.46–0.98	0.26–0.76
2			
MV RR	0.77	0.63	0.83
95% CI	0.52–1.12	0.40–0.99	0.50–1.38
>2			
MV RR	0.42	0.58	0.34
95% CI	0.13–1.33	0.28–1.19	0.12–0.92

Cauliflower, servings/mo	Broccoli, servings/wk <1	1	>1
c2			
MV RR	1.0†	0.58	0.74
95% CI	—	0.32–1.07	0.36–1.54
2			
MV RR	0.76	0.57	0.42
95% CI	0.54–1.07	0.36–0.90	0.21–0.84
>2			
MV RR	1.02	0.73	0.55
95% CI	0.55–1.87	0.48–1.10	0.34–0.90

*MV RRs are adjusted for age, pack-years of cigarette smoking (i.e., number of packs smoked per day x number of years of smoking), current smoking status, geographic region, total fluid intake, and caloric intake.

†Referent.

DISCUSSION

After we controlled for smoking and other risk factors for bladder cancer, a weak and nonsignificant inverse association was observed between total fruit and vegetable intake and bladder cancer risk in this cohort study of men. Intake of cruciferous vegetables was inversely associated with bladder cancer risk, and this result was independent of total vegetable intake. Other groupings of vegetables were not associated with the risk of bladder cancer.

In epidemiologic studies, null associations can arise in situations where the range of exposure is too small and there is insufficient power to detect an association. As shown in Table 1, the contrast between high and low consumption (difference between high and low medians) was far greater for total vegetable intake (4.8 servings/day) than for cruciferous vegetable intake (approximately 1 serving/day). For yellow, green leafy, and cruciferous vegetables, the contrasts were similar (approximately 1 serving/day). Therefore, it is unlikely that the null associations for groupings other than cruciferous vegetables were a result of a limited range of intake or misclassification.

Dietary assessment methods used in previous studies have often not been sufficiently comprehensive to estimate total fruit or vegetable intake. Only three case-control studies *(14,29,30)* and two cohort studies *(13,17)* have had data available to evaluate the relationship between total fruit or vegetable intake and bladder cancer risk. Total fruit intake *(30)* and total fruit and vegetable intake in men only (29) were inversely related to bladder cancer risk in two of the three case-control studies. Both cohort studies observed an inverse association for total fruit and bladder cancer risk with the use of 24-hour recalls (13) and FFQs *(17);* however, no association was reported for total fruit and vegetable intake [*(17);* vegetables were not measured in *(13)*].

To our knowledge, only one study *(7),* published in 1979, previously examined the association between cruciferous vegetable intake ***per se*** and bladder cancer risk. The reported association for that study was inverse (RR = 0.75 for high versus low consumption) but not statistically significant. Two additional studies *(8,9)* have found statistically significant inverse associations between dark green vegetable consumption and bladder cancer risk and, although one study did not specify the individual vegetables comprising "dark green vegetables" *(8),* broccoli was included in the other *(9).* One cohort study of 71 cases *(17)* did not report an association between "dark green vegetable'' intake (other leafy greens, broccoli, and Brussels sprouts) and bladder cancer risk.

Cruciferous vegetables of the genus and species ***Brassica oleracea,*** which include broccoli, cabbage, cauliflower, Brussels sprouts, kale, collard, and kohlrabi, have been widely studied for their anticarcinogenic properties in experimental studies *(31–33)* and have been associated with reduced cancer risk *(16,34).* Consumption of cruciferous vegetables induces detoxification enzymes in animal tissues *(35–37)* and stimulates metabolism of drugs and other xenobiotics in humans *(38,39).* Extracts of cruciferous vegetables have led to the identification of numerous

Table 5. Relative risks (RRs) and 95% confidence intervals (95% CIs) of incident bladder cancer by categories of total cruciferous vegetable intake, stratified on the basis of smoking status*

Smoking status	Cruciferous vegetable intake, servings/wk <1.5	1.5–2.5	2.6–4.4	≥4.5	Two-sided P for trend
Never smokers					
No. of cases	22	14	15	6	
RR† (95% CI)	1.0 (referent)	0.67 (0.34–1.32)	0.71 (0.36–1.38)	0.26 (0.10–0.65)	005
Past smokers					
No. of cases	40	26	42	28	
RR† (95% CI)	1.0 (referent)	0.70 (0.43–1.15)	1.11 (0.71–1.72)	0.70 (0.43–1.15)	34
Current smokers					
No. of cases	14	12	14	8	
RRP (95% CI)	1.0 (referent)	1.06 (0.49–2.30)	1.22 (0.57–2.60)	0.89 (0.36–2.17)	83

'Smoking information was missing for 11 cases

†Adjusted tor age. pack-years of cigarette smoking (i e number or packs smoked per day x number of years of smoking), except in never smoking model geographic region. total fluid intake. and caloric intake

Table 6. Relative risks (RRs) and 954 confidence intervals (95% CIs) of incident bladder cancer by quintiles of carotenoid intake estimated from the food-frequency questionnaire"

Carotenoid intake	Quintiles of intake 1	2	3	4	5	Two-sided P for trend
α-Carotene, μg/day	292	473	634	1012	1888	
No. of cases	48	58	50	*31*	59	
Person-years	87 100	87 814	86831	86 90}	86 809	
RR	1.0	1.20	0.97	0.68	0.97	.43
MV RR (95% CI)	1.0 (referent)	1.27 (0.86–1.86)	1.05 (0.70–1.56)	0.75 (0.49–1.16)	1.13(0.76–1.66)	.94
β-Carotene, μg/day	2046	3134	4223	5794	9202	
No. of cases	43	55	52	51	51	
Person-years	88 144	87512	86 960	86 825	86013	
RR	1.0	1.16	1.02	0.91	0.84	.15
MV RR (95% CI)	1.0 (referent)	1.21 (0.81–1.81)	1.07 (0.71–1.61)	1.00 (0.66–1.50)	0.94 (0.62–1.42)	.38
Lycopene, μg/day	3415	6156	8682	12 199	18 892	
No. of cases	44	52	58	52	46	
person-years	86 968	87 495	87212	87 095	86 685	
RR	1.0	1.27	1.39	1.22	1.03	.71
MV RR (95% CI)	1.0 (referent)	1.28 (0.85–1.91)	1.40(0.94–2.07)	1.22 (0.81–1.82)	0.98 (0.65–1.49)	.54
Lutein, μg/day	1296	2279	3181	4344	6845	
No. of cases	57	48	53	45	49	
person-years	87 246	87 182	87 400	86 759	86 868	
RR	1.0	0.82	0.88	0.75	0.80	.28
MV RR (95% CI)	1.0 (referent)	0.83 (0.56–1.22)	0.89 (0.61–1.30)	0.77 (0.52–1.14)	0.81 (0.55–1.19)	.31
β-Cryptoxanthin, μg/day	10.9	33.2	56.2	92.4	174.8	
No. of cases	56	46	53	34	63	
Person-years	86 794	87 372	87 527	87 154	86 609	
RR	1.0	0.84	0.88	0.54	0.89	.53
MV RR (95% CI)	1.0 (referent)	0.91 (0.62–1.35)	0.98 (0.67–1.43)	0.62 (0.41–0.96)	1.04 (0.72–1.51)	.90

*RRs are adjusted for age; multivariate RRs (MV RRs) are adjusted for age, pack-years of cigarette smoking (i.e., number of packs smoked per day x number of years of smoking), current smoking status, geographic region, total fluid intake, and caloric intake.

compounds, e.g., isothiocyanate sulforaphane *(40),* that are capable of inducing phase 2 detoxifying enzymes ***in vitro.*** Therefore, one possible mechanism whereby an increase in cruciferous vegetable intake protects the bladder epithelium from carcinogens is by enhancing detoxification of xenobiotics prior to excretion, although other mechanisms are plausible.

In a stratified analysis, we observed a strong inverse association between cruciferous vegetable intake and bladder cancer in nonsmokers and weak nonsignificant inverse associations in past and current smokers. The inverse association in nonsmokers indicates that residual confounding by smoking is unlikely to be responsible for the overall inverse association observed between cruciferous vegetable intake and risk of bladder cancer, yet, because smokers are constantly metabolizing and excreting carcinogens obtained from smoke *(41),* we would have expected them to benefit the most from faster metabolism of carcinogens (assuming that phytochemicals in cruciferous vegetables are able to activate detoxifying enzymes). Although the RRs related to Cruciferous vegetable consumption were stronger among nonsmokers, the test for statistical multiplicative interaction was not statistically significant. More data are needed to determine whether smoking status modifies the inverse association between cruciferous vegetable intake and risk of bladder cancer.

Of the cruciferous vegetables, broccoli and cabbage were independently related to the risk of bladder cancer in this study. Increasing broccoli intake was associated with decreasing risk of bladder cancer in each stratum of cabbage intake, and a similar pattern was observed for cabbage across broccoli intake. After we controlled for broccoli intake, cauliflower intake was no longer Significantly associated with bladder cancer risk. Although coleslaw and sauerkraut are made from cabbage, neither of these two vegetables was associated with bladder cancer risk, even before adjustment for broccoli intake. Measurement error could explain some of these differences if some vegetables are reported with less accuracy than others, resulting in attenuated associations in the poorly measured vegetables. This could explain the lack of association for coleslaw and sauerkraut intake [our validation study reported a deattenuated correlation between an FFQ and dietary records of **.37** for coleslaw and an observed correlation of .21 for sauerkraut *(24)*] but not for Brussels sprouts intake, inasmuch as our validation study indicates that it is measured with similar accuracy as broccoli [deattenuated correlations: .51 for Brussels sprouts compared with .46 for broccoli *(24)*]. Because the ranges of intake for individual cruciferous vegetables were similar, with the exception of broccoli intake, which had a wider range, associations are not likely to be the result of power differences. Alternatively, pickling of cabbage to make sauerkraut may destroy important phytochemicals or create undesired ones ***(42)*** and influence the relation to bladder cancer risk.

We cannot rule out the possibility that findings from this study are a consequence of multiple testing. We performed more than 50 tests (including tests on individual fruits and vegetables), thus increasing the probability of finding a significant result by "chance" with each additional test. However, given that the vegetables with significant associations were from a common family (cruciferae) and that there is plausible biologic evidence to support this finding, it is unlikely that our results were chance findings.

We did not observe a relationship between yellow vegetable

intake or carrot intake alone and bladder cancer risk. Two case–control studies *(7,8)* have reported a significant inverse association between carrot intake and bladder cancer risk, but two cohort studies *(16,17)* reported no association between yellow vegetable intake and bladder cancer risk. Carrots have often been associated with the risk of various cancers *(43)* and are of interest because of their high carotenoid content. We therefore examined the association between five important carotenoids and bladder cancer risk, but we observed no relationship for any of those carotenoids.

In this study, diet was determined before cancer diagnosis, with a time interval from 1 month to 10 years. Although we do not know at which point fruit and vegetable intake may influence bladder carcinogenesis, it is possible that, with longer follow-up, we would have observed different associations. However, restricting the analyses to men who had indicated in 1986 that their consumption of fruits and vegetables had not changed during the past 10 years did not affect the associations. We also repeated all of our analyses using cumulative averages of diet with updating of the 1990 and 1994 diet questionnaires to reduce within-person variation over the follow-up period. Since the associations in the restricted and in the updated analyses were similar to the main analyses, it is unlikely that a longer follow-up period would significantly alter our results.

More studies are needed to confirm findings from this study in men as well as in women. Because bladder cancer incidence rates are three to four times greater in men than in women, associations observed in men may not necessarily be generalized to women. Biologic responses to certain carcinogens may well vary by sex; thus, chemopreventive agents may be equally affected.

In this prospective study, we report a strong inverse association between the intake of cruciferous vegetables and bladder cancer risk. However, we did not observe a statistically significant relationship between total fruit and vegetable intake and incidence of bladder cancer after we controlled for potential confounders such as smoking status. The inverse association between cruciferous vegetable intake and bladder cancer risk was strongest in never smokers. Although confiiation in other prospective studies is required, data from this study suggest that high intake of cruciferous vegetables, such as broccoli, may substantially reduce bladder cancer risk.

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NOTES

Supported by Public Health Service grants CA55075 (National Cancer Institute) and HL35464 (National Heart. Lung, and Blood Institute), National Institutes of Health, Department of Health and Human Services; and by Special Institution Grant No. 18 from the American Cancer Society.

Manuscript received September 14, 1998; revised January 21, 1999 accepted January 28, 1999.