A Prospective Study of Cruciferous Vegetables and Prostate Cancer

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Abstract

High intake of cruciferous vegetables may offer some protection against prostate cancer, but overall data are inconclusive. Thus, we examined the association between cruciferous vegetable intake and risk of prostate cancer in the Health Professionals Follow-Up Study. Between 1986 and 2000, 2,969 cases of nonstage T1a prostate cancer were diagnosed in 47,365 men who completed dietary assessments in 1986, 1990, and 1994. We calculated the multivariate relative risk (RR) and 95% confidence intervals (CIs) using Cox regression. Overall, we found no appreciable association between baseline intake of cruciferous vegetables and risk of prostate cancer (RR, 0.93; 95% CI, 0.82–1.05, for ≥5 *versus* ≤1 serving/week; *P* for trend = 0.30), and only a slight suggestive association for organ-confined prostate cancer (RR, 0.88; 95% CI, 0.74–1.05; *P* for trend = 0.06). The inverse association was stronger for men under the age of 65 years (RR, 0.81; 95% CI, 0.64–1.02; *P* for trend = 0.02), especially for organ-confined cancers (RR, 0.72; 95% CI, 0.54–0.97; *P* for trend = 0.007). In addition, this inverse association was stronger when we restricted the analysis to men with more consistent intake of vegetables over the 10 years before 1986, when we limited the analysis to men who had had a prostate-specific antigen test, and when we considered an 8-year time lag. This study does not provide compelling evidence of a protective influence of cruciferous vegetables on prostate cancer risk. However, if cruciferous vegetables are protective early in prostate carcinogenesis, as suggested by proposed mechanisms, we may expect stronger associations, as observed, for more remote diet for prostate-specific antigen-detected early stage (organ-confined) cancers in younger men. In contrast, for advanced cancers in older men, which were probably initiated decades in the past, recent dietary intakes of cruciferous vegetables may be irrelevant. These findings suggest that future studies of cruciferous vegetables should focus on early stages of prostate cancer.

Introduction

Cruciferous vegetables (Brassica oleracea family) have received considerable scrutiny in cancer research because of putative protective properties. Specifically, breakdown products of glucosinolates from cruciferous vegetables increase levels of phase I and phase II xenobiotic metabolizing enzymes, thereby more rapidly eliminating potential DNA carcinogens (1). Some epidemiological studies suggest that greater intake of these vegetables may lower risk for several types of cancers (2). In a recent extensive review, Kristal and Lampe (3) concluded that the epidemiological literature provides modest support that high intake of cruciferous vegetables lowers risk of prostate cancer. They recommended that additional research is warranted because of inconsistencies in the findings.

An important unresolved issue concerns the relevant time period when cruciferous vegetables may act in the cancer process. The induction of xenobiotic metabolizing enzymes, which may protect against DNA damage, suggests that cruciferous vegetables may be most important early in prostate carcinogenesis. The time range from initiation to diagnosis in prostate carcinogenesis may cover several decades or more; because most studies have focused on diet relatively shortly before the diagnosis, an influence of remote diet can be easily missed. The ability or inability of studies to capture the relevant time that cruciferous vegetables are acting may contribute to the apparently conflicting results.

In the Health Professional Follow-Up Study cohort, we had reported previously no overall association between individual cruciferous vegetables and prostate cancer risk. That analysis was based on the initial dietary assessment in 1986 and on 773 incident cases diagnosed from 1986 to 1992 (4). We now report results on cruciferous vegetable intake based on multiple dietary assessments from 1986 to 2000 and on 2969 cases of prostate cancer. We took into account screening by prostate-specific antigen (PSA) and the timing of diet in relation to cancer diagnosis.

Materials and Methods

The Study Population. In 1986, 51,529 United States male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, aged 40–75 years, completed and returned a mailed questionnaire to initiate the Health Professionals Follow-up Study cohort. This cohort is predominantly Caucasian (>91%). Through this 1986 baseline questionnaire, we elicited information on age, marital status, height and weight, ancestry, medications, smoking history, disease history, physical activity, and diet. Every 2 years, we mailed to surviving cohort members questionnaires that elicited information on new medical diagnoses and on lifestyle factors. We updated diet through food frequency questionnaires administered every 4 years. Deaths among cohort members were reported by family

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members or by the postal system in response to the mailed questionnaires, or were ascertained through the National Death Index. Through the various methods used, we estimate having ascertained >98% of the deaths and 96% of the incident prostate cancers in this cohort. This cohort study is approved by the Human Subjects Committee of the Harvard School of Public Health.

The Food-Frequency Questionnaire. We used a semiquantitative food-frequency questionnaire to assess diet. This questionnaire (described in detail in Ref. 5), was first administered in 1986, and contained a list of 131 food and beverage items and an open-ended section. For each item listed, a commonly used unit or portion size was specified, and participants were asked how often, on average, over the past year, they consumed that amount of each item. Participants chose from among nine possible responses for frequencies, which ranged from never to six or more times per day. A similar dietary questionnaire was administered to the cohort in 1990 and 1994. We computed nutrient intakes by multiplying the consumption frequency of each unit of food by the nutrient content of the specified portions, using composition values from United States Department of Agriculture sources supplemented with other data. The specific cruciferous vegetable items (six questions) assessed were (1/2 cup serving size) broccoli, cabbage or coleslaw, sauerkraut, cauliflower, Brussels sprouts, and kale, mustard or chard greens.

We evaluated the validity of nutrient and food consumption measured by the questionnaire among a sample of 127 cohort members from the Boston area (5, 6). The mean correlation coefficients between intakes determined by two 1-week diet records and the food-frequency questionnaire (deattenuated for week-to-week variation in the diet records) were 0.65 for nutrients and 0.63 for specific foods. The mean intake for total cruciferous vegetables was 0.26 servings/day based on diet records and 0.38 servings/day based on the questionnaire. For specific cruciferous vegetables, the deattenuated correlations were 0.46 for broccoli, 0.37 for coleslaw, 0.51 for Brussels sprouts, and 0.25 for kale, chard (not a crucifer), and mustard greens (asked together). For other cruciferous vegetables, the week-to-week variation in dietary record intakes was too high to allow reliable estimates.

Assessment of Other Exposure Information. On the 1986 baseline questionnaire, we asked the men to report their current height and weight, and weight at age 21. Current weight was also assessed on each biennial questionnaire. We used body mass index (kg/m^2) to estimate total adiposity (7). To assess physical activity, we used MET hours/week calculated from a list of activities reported in 1986 and updated every 2 years thereafter (8). One MET hour is the metabolic equivalent of sitting at rest for 1 h. Detailed lifetime tobacco use was assessed at baseline, and current smoking status was assessed every 2 years through the follow-up questionnaires. We began assessing screening for prostate cancer by PSA on the biennial questionnaires beginning in 1994. In 1990, to assess family history, we asked the men whether their father or any brothers had had a diagnosis of prostate cancer.

Identification of Cases of Prostate Cancer. On the follow-up questionnaires, the study participant (or next of kin for decedents) reported any new diagnosis of prostate cancer. For newly reported cases, we then asked for permission to obtain hospital records and pathology reports so we could obtain additional details regarding the diagnosis and treatment. Study investigators used the staging information received from any procedures or tests conducted during the initial diagnosis and treatment including prostatectomies and bone scans. From 1986 to the end of this study period (January 31, 2000), we documented 2969 prostate adenocarcinoma cases after we excluded 68 cases of stage T1a cancers (incidental histological cancer found in ≤5% of tissue resected). The stage T1a cancers are relatively innocuous, are especially prone to detection bias, and encompass only 2% of the total diagnosed cases. Of the 2969 cases, we were able to document ~90% using medical records and pathology reports; for most of remaining 10%, participants provided information regarding the diagnosis and subsequent treatment. Because a diagnosis of prostatic adenocarcinoma was confirmed for 99% of the cases when we acquired medical records, we considered as cases all of the men who reported prostate cancer, except for the few excluded by medical records.

Data Analysis. We excluded from the analysis men who reported cancer at baseline (other than nonmelanoma skin cancer), and men who inadequately completed the dietary questionnaire [≥70 left blank, or reported intake of >17,600 kilojoules (4200 kcal) or <3,350 kilojoules (800 kcal) per day]. There were 47,365 participants remaining after these exclusions. The men were followed beginning on the month of return of the baseline questionnaire until the month of diagnosis of prostate cancer, month of death from other causes, or the end of the study period (January 31, 2000). The endpoints were total prostate cancer (excluding stage T1a tumors), organ-confined prostate cancer, and advanced cancers [those extending locally or distally into local (stage C2) or distal (stage D) organs at the time of diagnosis, or that were fatal by 2000].

The main exposure variable was total cruciferous vegetable intake (see "Diet" section above). We also considered the individual cruciferous vegetables. Because the induction period for any relationship between cruciferous vegetables and prostate cancer risk is not known, we conducted analyses using both the baseline (1986) dietary intake and the cumulatively updated diet, which is the average of intakes based on all of the available dietary questionnaires completed up to the time period of risk. Relative to cumulatively updated diet, the baseline assessment assigns greater weight to more remote diet. We also conducted alternative analyses limited to men who at baseline reported that their intake of vegetables had not changed substantially in the prior 10 years. To examine the temporal aspects of the relationships between cruciferous vegetable intakes and prostate cancer risk, we performed three lagged analyses. Recent diet was examined by using a 0–4-year lag analysis; for example, 1986 diet was used for the follow-up period from 1986 to December 1989; 1990 diet was used for the follow-up period from 1990 to December 1993, and so forth. For the 4–8-yar lagged analysis, the 1986 diet was used for follow up from 1990 to December 1993, the 1990 diet was used for follow-up from 1994 to December 1998; and the 1994 diet was used for follow-up from 1998 to December 2000. For the ≥8-year lagged analysis, 1986 diet was used for follow-up from 1994 to 2000.

Finally, we conducted an analysis restricted to men who reported that they had had at least one PSA test during the time period from 1994, the year PSA was first assessed, to 2000. This analysis was limited to the 1994–2000 period, because we only had prospective data on PSA beginning in 1994.

We computed relative risks (RRs) defined as the incidence rate of disease in one category (*e.g.*, high intake of cruciferous vegetables) divided by the incidence rate in a reference category (*e.g.*, low intake). We used the Mantel-Haenszel summary estimator to adjust for age (across 5-year categories). We used Cox proportional hazards modeling to control for multiple variables simultaneously and to compute 95% confidence intervals (95% CI). Age (1-year) and time period (2-year inter-

Table 1 Relative risk (RR) and 95% confidence interval (CI) of prostate cancer by intake of cruciferous vegetables in 47,365 men of the Health Professionals Follow-Up Study (HPFS) from 1986–2000

	Cruciferous Vegetables (1986 intake)[a]					*P* (trend)
	≤1/wk	1.1–2/wk	2.1–3/wk	3.1–5/wk	>5/wk	
Total prostate cancer (*n*)	496	686	504	678	605	
Age-adjusted RR	1.0	1.01	0.95	0.94	0.93	0.12
MV-adjusted RR[b]	1.0	0.99	0.93	0.94	0.93	0.30
95% CI		0.88–1.12	0.82–1.06	0.83–1.06	0.82–1.05	
MV-adjusted RR[b]	1.0	0.99	0.93	0.93	0.91	0.13
+Fruits and Veg 95% CI		0.88–1.12	0.82–1.06	0.82–1.05	0.79–1.04	
Organ-confined prostate cancer (*n*)	274	414	289	382	322	
Age-adjusted RR	1.0	1.10	0.98	0.96	0.90	0.03
MV-adjusted RR[b]	1.0	1.07	0.95	0.93	0.88	0.06
95% CI		0.91–1.25	0.80–1.13	0.79–1.09	0.74–1.05	
MV-adjusted RR[b]	1.0	0.99	0.94	0.94	0.92	0.13
+Fruits and Veg 95% CI		0.88–1.12	0.82–1.07	0.83–1.06	0.80–1.05	
Extraprostatic prostate cancer (*n*)	74	89	85	90	111	
Age-adjusted RR	1.0	0.88	1.07	0.84	1.14	0.41
MV-adjusted RR[b]	1.0	0.86	1.04	0.84	1.06	0.38
95% CI		0.63–1.18	0.76–1.44	0.61–1.16	0.77–1.45	
MV-adjusted RR[b]	1.0	0.85	1.03	0.82	1.00	0.76
+Fruits and Veg 95% CI		0.62–1.17	0.74–1.42	0.59–1.13	0.71–1.40	

[a] Combined intake of broccoli, cabbage or coleslaw, sauerkraut, cauliflower, Brussels sprouts, and kale, mustard, or chard greens. The standard servings size for each was ½ cup.
[b] Multivariate (MV) model included: body mass index (BMI) at age 21, BMI in 1986, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, vigorous physical activity, and intakes of total calories, red meat, processed meat, fish, α-linolenic acid, calcium, and tomato sauce. Age and time period were strata variables in the Cox proportional hazards model.

vals) were controlled for as stratification variables in the Cox model. The following covariates were included in the models: body mass index at age 21 years, body mass index in 1986, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, vigorous physical activity, and intakes of total calories. We also included nutrients and foods that are associated with increased risk of total or advanced prostate cancer in this population, as well as in additional studies (4, 9–11), including red meat, processed meat, fish, α-linolenic acid, calcium, and tomato sauce. We updated modifiable variables. In an additional model, we included total fruit and vegetable intake to determine whether any influence of cruciferous vegetables was specific to this group or to fruit and vegetable intake in general. We tested for trend across categories controlling for multiple covariates by modeling the median values of quintiles or categories of dietary intake as a continuous variable in the multivariate model. All of the reported *P*s are two-sided.

Results

Age-Adjusted and Multivariate Analyses. Table 1 shows the results for total cruciferous vegetables in relation to total, extraprostatic, and organ-confined prostate cancer risk using baseline (1986) intakes. The results for the age-adjusted and the multivariate analyses were similar, suggesting that the other variables did not cause appreciable confounding of the cruciferous vegetable results. No appreciable association was observed between cruciferous vegetable intake and risk of total or advanced prostate cancer, and a modest association ($P = 0.06$) was observed with organ-confined prostate cancer. Additional adjustment for total fruits and vegetables did not change the results for total cruciferous vegetables appreciably. Total fruit and vegetable intake itself was not associated with risk of total prostate cancer [multivariate RR (also adjusting for cruciferous vegetables) = 1.07 (95% CI, 0.92–1.24) for the high *versus* low quintile of intake]. Using cumulatively updated intakes, the associations for total prostate cancer were similar but somewhat weaker [multivariate RR, 0.94 for >5 servings/week *versus* ≤1 serving/week; 95% CI, 0.81–1.08; *P*(trend) = 0.69].

Age- and Family History-Stratified Analyses. We analyzed the relationships between cruciferous vegetable intake and prostate cancer risk among younger (<65 years at diagnosis) and older (≥65 years at diagnosis) men. Table 2 shows evidence of an inverse association only in the younger men, particularly for organ-confined cancers. Using cumulative-updated analysis, the association for total prostate cancer for men <65 years old was similar but somewhat weaker and lost statistical significance [multivariate RR, 0.84; 95% CI, 0.66–1.08; *P*(trend) = 0.29]. The test for interaction with age [based on the cross-product term for age (0 = young and 1 = old) and cruciferous vegetable intake (continuous)] yielded a *P* of 0.10 for total prostate cancer, 0.08 for organ-confined cancer, and 0.40 for extraprostatic cancer. Further restricting the population to men under the age of 60 years provided similar results as for men <65 years. There was no evidence that the relationship between total prostate cancer and cruciferous vegetable intake varied among men with a positive family history of prostate cancer [multivariate RR, 0.93; 95% CI, 0.63–1.37; *P*(trend) = 0.95] or among those without a history [multivariate RR, 0.91; 95% CI, 0.79–1.04; *P*(trend) = 0.27].

Cruciferous Vegetable Type. For total prostate cancer, none of the specific crucifera were significantly related to risk (all *P*s ≥0.19). For men <65 years, none of the specific cruciferous vegetables were significantly related to lower risk, but most had weak inverse associations. The strongest association was observed for cauliflower intake [RR, 0.84; 95% CI, 0.71–1.00, for >1 serving/week *versus* <1 serving/month; *P*(trend) = 0.06] and slight nonsignificant inverse association was observed for intakes of broccoli [RR, 0.87; 95% CI, 0.73–1.05 for >2 servings/week *versus* <1 serving/week; *P*(trend) = 0.63] and cabbage intake [RR, 0.91; 95% CI, 0.71–1.17 for >1 serving/week *versus* <1 serving/month; *P*(trend) = 0.34].

Table 2 Relative risk (RR) and 95% confidence interval (CI) of prostate cancer by intake of cruciferous vegetables in Health Professionals Follow-Up Study (1986–2000)

	Cruciferous vegetables (1986 intake)					*P* (trend)
	≤1/wk	1.1–2/wk	2.1–3/wk	3.1–5/wk	>5/wk	
Total prostate cancer						
Age <65 (*n*)	163	248	183	202	166	
RR[a]	1.0	1.03	0.97	0.83	0.81	0.02
95% CI		0.85–1.27	0.78–1.20	0.67–1.03	0.64–1.02	
Age ≥65 (*n*)	333	438	321	476	439	
RR[a]	1.0	0.97	0.91	0.98	0.98	0.72
95% CI		0.83–1.12	0.77–1.06	0.85–1.13	0.84–1.14	
Organ-confined prostate cancer						
Age <65 (*n*)	105	162	105	127	92	
RR[a]	1.0	1.04	0.87	0.82	0.72	0.007
95% CI		0.81–1.33	0.66–1.15	0.63–1.07	0.54–0.97	
Age ≥65 (*n*)	169	252	184	255	230	
RR[a]	1.0	1.08	0.99	0.99	0.96	0.60
95% CI		0.89–1.32	0.80–1.23	0.81–1.21	0.78–1.19	
Extraprostatic prostate cancer						
Age <65 (*n*)	18	34	34	19	27	
RR[a]	1.0	1.22	1.36	0.62	0.90	0.25
95% CI		0.69–2.17	0.76–2.44	0.32–1.21	0.48–1.70	
Age ≥65 (*n*)	56	55	51	71	84	
RR[a]	1.0	0.72	0.88	0.93	1.10	0.07
95% CI		0.49–1.06	0.59–1.30	0.64–1.33	0.77–1.59	

[a] Multivariate model included same variables as in Table 1.

Analyses Restricted to Men Who Had a PSA Test. We conducted an analysis restricted to men who had undergone a PSA test to reduce the potential for detection bias. In this analysis, we found that higher intakes of cruciferous vegetables were related to a lower risk of prostate cancer (Table 3). The results were similar for the young and older age strata. The great majority of PSA-detected cancers are organ-confined. Thus, not surprisingly, the results were similar when restricted to organ-confined prostate cancer [multivariate RR, 0.76 for >5 servings/week *versus* ≤1 serving/week; 95% CI, 0.61–0.96; *P*(trend) = 0.02].

Time Lagged Analyses. We conducted three lagged analyses to examine the temporal aspects of the relationship of cruciferous vegetables and prostate cancer. Using a 0–4-year lag, the multivariate RR for high *versus* low intake of cruciferous vegetables was 1.01 [95% CI, 0.89–1.13; *P*(trend) = 0.55] for total prostate cancer and 0.98 [95% CI, 0.83–1.16; *P*(trend) = 0.25] for organ-confined prostate cancer. For the 4–8-year lagged analysis, the multivariate RR was 0.90 [95% CI, 0.79–1.03; *P*(trend) = 0.04] for total prostate cancer and 0.87 [95% CI, 0.73–1.04; *P*(trend) = 0.002] for organ-confined prostate cancer. For the ≥8-year lagged analysis, the multivariate RR was 0.87 [95% CI, 0.73–1.04; *P*(trend), 0.64] for total prostate cancer and RR = 0.81 [95% CI, 0.65–1.02; *P*(trend) = 0.37] for organ-confined prostate cancers.

Long-Term Consistent Intake. We excluded from our analysis men who reported on the baseline questionnaire that their intake of vegetables had increased significantly in the previous 10 years to form a group more likely to have consistently high intakes of cruciferous vegetables in the past. In this analysis (Table 4), a somewhat stronger inverse association was observed with risk of prostate cancer than for the overall analysis (compare with Table 1), especially for organ-confined prostate cancer.

Discussion

In this large prospective study, we found only a weak and nonstatistically significant inverse association between cruciferous vegetable intake and risk for prostate cancer. However,

Table 3 Relative risk (RR) and 95% confidence interval (CI) of prostate cancer by intake of cruciferous vegetables limited to men who reported that they had a prostate-specific antigen test (1994–2000)

	Cruciferous vegetables (1986 intake)					*P* (trend)
	≤1/wk	1.1–2/wk	2.1–3/wk	3.1–5/wk	>5/wk	
Total prostate cancer (*n*)	238	317	259	341	263	
RR[a]	1.0	0.97	0.91	0.92	0.77	0.03
95% CI		0.81–1.15	0.76–1.10	0.78–1.10	0.64–0.93	
Age <65 (*n*)	81	120	90	109	75	
RR[a]	1.0	1.04	1.00	1.02	0.79	0.22
95% CI		0.78–1.40	0.73–1.36	0.76–1.39	0.56–1.10	
Age ≥65 (*n*)	157	197	169	232	188	
RR[a]	1.0	0.93	0.87	0.89	0.77	0.08
95% CI		0.75–1.16	0.69–1.09	0.72–1.10	0.61–0.96	

[a] Multivariate model included same variables as in Table 1.

Table 4 Relative risk (RR) and 95% confidence interval (CI) of prostate cancer by intake of cruciferous vegetables excluding those who reported increased vegetable intake in last 10 years at 1986

	Cruciferous vegetables (1986 intake)					*P* (trend)
	≤1/wk	1.1–2/wk	2.1–3/wk	3.1–5/wk	>5/wk	
Total prostate cancer (*n*)	379	437	308	380	266	
RR[a]	1.0	0.89	0.87	0.88	0.84	0.14
95% CI		0.77–1.02	0.75–1.02	0.76–1.02	0.71–0.99	
Organ-confined (*n*)	212	260	189	201	132	
RR[a]	1.0	0.93	0.95	0.84	0.76	0.02
95% CI		0.78–1.12	0.78–1.17	0.69–1.03	0.61–0.96	
Extraprostatic (*n*)	60	56	45	55	51	
RR[a]	1.0	0.72	0.76	0.77	0.91	0.92
95% CI		0.50–1.05	0.51–1.13	0.53–1.13	0.61–1.35	

[a] Multivariate model included same variables as in Table 1.

the inverse association was strengthened when we used the baseline dietary assessment rather than updated analysis, when we excluded men who had reported an increase in their vegetable intake in the 10 years before 1986, when we allowed a 4- or 8-year time lag between the dietary assessment and period of risk, and when the analysis was restricted to the population that had received PSA screening. Furthermore, the inverse associations were stronger for younger men and for organ-confined cancers. These patterns might be expected for factors that influence early stages (initiation) of prostate carcinogenesis. In contrast, for advanced cancers in older men, whose cancers had probably been initiated decades in the past, no association was observed. Whereas this interpretation should be tempered by the overall weak findings, the consistent pattern reduces that possibility that all of these findings arose through chance. An alternative explanation for the apparently stronger influence on organ-confined cancers is that cruciferous vegetables influence primarily a subgroup of less aggressive prostate cancer.

Our findings suggesting that cruciferous vegetables are most important in early stages are also compatible with the postulated mechanisms. Although some evidence indicates that cruciferous vegetables may influence later stages of carcinogenesis, most research has centered on how breakdown products of glucosinolates (*e.g.,* isothiocyanates) influence levels of phase I and phase II biotransformation enzymes (1). For example, cruciferous vegetables contain high levels of the isothiocyanate sulforaphane, which is a very potent phase II enzyme-inducing agent (12). Sulforaphane was shown recently to induce phase II enzyme expression and activity significantly in human prostatic cells *in vitro* (13). In prostate cancer, the most common molecular genetic event is the silent expression of *GSTP1* through the methylation of deoxycytidine residues in CpG islands of the *GSTP1* gene (14, 15). This event occurs early as indicated by its presence in all cases of high-grade prostatic intraepithelial neoplasia and in most prostate cancers regardless of grade and stage (16). By up-regulation of the phase II enzymes (*e.g.,* other glutathione *S*-transferases), cruciferous vegetables have been hypothesized to protect against the early stages of prostate cancer (13).

If the modest inverse associations we observed are caused by the activation of phase II enzymes, the potential risk reduction might be even stronger than observed. First, although the associations became consistently stronger in analyses that account for the long time lag between early carcinogenic events and the end point, associations could have possibly become even stronger with increasing time lags. Secondly, although our assessment of cruciferous vegetables appeared reasonable based on our validation study, some degree of measurement error is inevitable and would tend to attenuate associations. However, we have reported strong inverse associations for high *versus* low cruciferous vegetable intake (independent of total vegetable intake) and bladder cancer risk in this cohort (RR, 0.49; 95% CI, 0.32–0.75; Ref. 17), although not for lung cancer (RR, 1.11; 95% CI, 0.76–1.64; Ref. 18), suggesting that we can assess cruciferous with sufficient precision to detect meaningful associations. Finally, although we had a reasonable range of intakes to examine associations, stronger associations could possibly be observed with a wider range of intakes.

Another factor that influences our interpretation is that myrosinase, the plant enzyme that converts glucosinolates into the active compounds, is inactivated by cooking. In one study, volunteers who consumed uncooked watercress excreted isothiocyanates in the range of 17.2–77.7% of the total glucosinolates consumed, but when the myrosinase activity was completely inactivated by cooking, excretion was reduced to 1.2–7.3% of the total (19). Another study found that the bioavailability of isothiocyanates was approximately three times greater in raw than in cooked broccoli (20). Thus, although the men in our study who reported eating 5+ serving per week of cruciferous vegetables were likely on average to have higher intakes of isothiocyanates than those consuming <1 serving per week, much of this intake is from cooked vegetables. We could not directly estimate actual intake of isothiocyanates.

Few epidemiological studies, mostly case-control studies, have examined comprehensively the relationship between cruciferous vegetable intake and prostate cancer risk. In a case-control study by Cohen *et al.* (21), men who consumed ≥3 servings of cruciferous vegetables per week had an odds ratio (OR) of 0.54 (95% CI, 0.40–0.76) compared with men who consumed <1 serving per week. This study was restricted to men from ages 40 to 64. Another large case-control study of men with age range <84 years found an overall OR of 0.76 (95% CI, 0.61–1.00) for the higher *versus* low quintile of intake; the association was even stronger for stage C and D cases (OR, 0.61; 95% CI, 0.42–0.88; Ref. 22). Another case-control study conducted in Hawaii reported an OR of 0.8 comparing high to low quartiles for men <70 years of age and a corresponding OR of 1.1 for older men (23). In a case-control study conducted in Canada, cruciferous vegetables were inversely associated with risk [OR, 0.67 (95% CI, 0.54–0.92) and OR, 0.80 (95% CI, 0.59–1.10) for the third and fourth quartiles, respectively, compared with the lowest quartile of intake; *P*(trend) <0.05; Ref. 24]. Another large case-control study ($n = 1623$ cases and 1623 controls) conducted in Canada (25) found only a weak inverse association between high intake of

cruciferous vegetables and prostate cancer risk (OR, 0.9; 95% CI, 0.7–1.1); however, this study did not report what cruciferous vegetables were included. The two studies (23, 25) with the weakest association may have had a limited assessment of cruciferous vegetables, although this was not entirely clear from the report. The case-control studies offer moderate support of a protective influence of cruciferous vegetables. However, nonresponse may bias results, because high consumption of vegetables may possibly be associated with greater likelihood to participate as controls in case-control studies.

Prospective data are quite limited. One study that was limited by assessment of mortality only (assessed through death certificates), small numbers of deaths ($n = 149$), and limited assessment of cruciferous vegetables (*i.e.,* broccoli not assessed) found a nonsignificant slightly higher risk associated with greater intake (26). A cohort study from the Netherlands reported on 610 men with prostate cancer (27). That study reported a borderline statistically significant association [P(trend) = 0.06] trend with lower risk of prostate cancer associated with higher intakes of cruciferous vegetables (RR, 0.80; 95% CI, 0.59–1.10).

The relatively weak but suggestive findings from epidemiological studies may be a consequence of the difficulty in studying factors that may act early in prostate carcinogenesis. Prostate cancer is likely to be influenced by hormonal influences during puberty and adolescence. Prostatic intraepithelial neoplasia is prevalent in 10% of men by age 30 and small foci of cancer in 10% of men by age 40 (28), but the median age of death from prostate cancer is 78 years. Thus, the average time from the earliest initiation events to terminal events may be ≥60 years. Epidemiological studies that assess diet shortly before late events (*e.g.,* symptomatic or metastatic disease, or mortality) are unlikely to detect associations related to early carcinogenic events because the diets of individuals may change over time. With the onset of PSA screening, prostate cancers are diagnosed at considerably younger ages and at earlier, organ-confined stages. The inverse associations we observed with cruciferous vegetables were stronger in younger men diagnosed with organ-confined, PSA-detected cancers, and with evidence of more stable long-term dietary patterns. The study with the strongest observed association between cruciferous vegetables and prostate cancer risk was conducted in younger men (<65 years), and the majority of cancers were PSA-detected and organ-confined (21). In contrast, a prospective study that examined mortality from prostate cancer as the sole end point was one of the few studies that did not find an inverse association (26). Overall, these data are consistent with an early influence of cruciferous vegetables.

Several public health implications are suggested by our results. Although the overall associations were weak, and significant findings only emerged in subgroup analyses, the findings support recommendations to increase intake of vegetables, including those of the Brassica family. Although not conclusive, at least some evidence suggests benefits against prostate, bladder, lung, and colorectal cancers, as well as non-Hodgkin's lymphoma (2, 3, 17, 18, 21, 22, 27, 29). Efficacy against many cancers is plausible, because the metabolic breakdown products of glucosinolates may influence levels of xenobiotics-metabolizing enzymes that could protect diverse tissues against DNA damage from many carcinogens (1). Our results also suggest that a protective effect against prostate cancer may emerge only after many years. Thus, cruciferous vegetables may be optimally beneficial when consumed at relatively young ages.

Our results also have implications for additional research. Although not definitive, the suggestive associations for prostate cancer should encourage additional epidemiological, clinical, and mechanistic research. Epidemiological studies need to better focus on diet earlier in life and on the time lag between exposure and end point. Our results, based on ~3000 cases and multiple assessments of diet, provide strong evidence against a benefit on cancer end point (especially clinically advanced disease) for diet intake within the past decade. Future epidemiological and intervention studies should take this time relationship into account or they may potentially produce false negative results. Further insight may also be provided by studies that examine simultaneously crucifera intake and various identified genotypes of phase II enzymes (*e.g.,* GSTM1 null genotype), because associations may be stronger with certain genotypes as suggested for lung (30) and colorectal neoplasms (31).

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