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Original Article

Consumption of cruciferous vegetables and the risk of bladder cancer in a prospective US cohort: data from the NIH-AARP diet and health study

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Abstract: Background: Abundant pre-clinical data suggest that consumption of cruciferous vegetables might protect against bladder cancer. While small-scale clinical evidence supports this hypothesis, population-level data is lacking. We tested the hypothesis that consumption of cruciferous vegetables is associated with a lower risk of bladder cancer in a large population-based study. Methods: We investigated the association between dietary consumption of cruciferous vegetables and the risk of bladder cancer in the NIH-American Association of Retired Persons (AARP) Diet and Health Study. Diet at baseline was collected with self-administered food-frequency questionnaires. Bladder cancer diagnoses were identified through linkage with state cancer registries. Hazard ratio (HR) and 95% confidence intervals (CI) were estimated with Cox proportional hazards models. Results: Our analysis included 515,628 individuals. Higher intake of cruciferous vegetables, both overall and when stratified by variety (broccoli vs. brussels sprouts vs. cauliflower), were not associated with bladder cancer risk for men or women. A history of smoking did not affect the results. Conclusions: Our study shows no association between dietary consumption of cruciferous vegetables and incident bladder cancer.

Keywords: Cruciferous vegetables, broccoli, bladder cancer, NIH-AARP, diet

Introduction

Tremendous interest exists in dietary interventions to reduce the development of cancer. Cruciferous vegetables are a family of vegetables that includes broccoli, cabbage, brussels sprouts, collard greens, kale, cauliflower, and turnips. In the past decade, studies have linked the consumption of cruciferous vegetables to reduced risk of cardiovascular mortality and development of Type II diabetes [1-3]. Based on promising pre-clinical data, cruciferous vegetables have emerged as a dietary substance that might also protect against cancer. Various studies, including: cross-sectional, case control, cohort, and prospective studies, also suggest that consumption of cruciferous vegetables may protect against development of several cancers, including: breast, lung, pancreatic, and prostate cancer [4-8].

Pre-clinical studies suggest that cruciferous vegetables may also protect against bladder cancer. Specifically, cruciferous vegetables are rich in isothiocyanates, compounds that have been shown to have anticarcinogenic effects against bladder cancer in animal models and in vitro studies [9-15]. Pre-clinical studies utilizing isothiocyanate in rat bladder cancer models demonstrated inhibition of bladder cancer development and progression [15]. Similarly, several other in vitro and in vivo studies have supported these results [16-18].

However, epidemiological studies intended to detect an association between cruciferous vegetable intake and bladder cancer in patients has shown conflicting results. Several small cohort and case control studies have found that cruciferous vegetables are associated with a decreased risk for bladder cancer [9, 19, 20], while others studies have found no association [9, 21, 22]. However, these studies were limited by relatively small sample sizes, thus lacking statistical power to detect an association between cruciferous vegetable consumption and bladder cancer risk.

We sought to clarify the conflicting evidence in the literature by exploring the relationship between cruciferous vegetable intake and bladder cancer based in a large United States population. We used data from the NIH-AARP Diet and Health Study, which provides dietary data on a prospective cohort including over 500,000 subjects. We tested whether consumption of the cruciferous vegetables broccoli, brussels sprouts, and cauliflower was associated with the risk of incident bladder cancer.

Methods

Study population

The NIH-American Association of Retired Persons (AARP) Diet and Health Study, initiated in 1995-1996, includes subjects (age 50-71) who lived in California, Florida, Pennsylvania, New Jersey, North Carolina, Louisiana, or in the cities of Atlanta or Detroit. After obtaining informed consent, 3.5 million AARP members were mailed baseline dietary questionnaires of which 567,169 (16.2%) were completed. The Special Studies Institutional Review Board of the US National Cancer Institute has reviewed and approved the NIH-AARP Diet and Health study. The data included in this study was obtained after formal review and approval of the research by the NIH-AARP Diet and Health Study (# 201410-0010). All data was de-identified by the NIH-AARP Diet and Health Study prior to provision to our site and was therefore ruled exempt from local IRB review.

Information on cancer stage was obtained from state cancer registries. For bladder cancer, we identified in situ, localized, low grade, high grade, advanced, and fatal bladder cancer. Fatal cases were those who died of bladder cancer during follow up.

From the 567,169 respondents who returned the baseline dietary questionnaire, we excluded those who withdrew from the study, those whose questionnaires were completed by proxy respondents, participants who had submitted duplicate questionnaires and participants with cancer diagnosed prior to study entry. After these exclusions, 515,628 individuals were included in our analysis.

Diet ascertainment

A self-administered food-frequency questionnaire (FFQ) was used to assess baseline diet based on reporting of 124 foods, including 23 vegetables or their derivatives, during the previous year. In regard to broccoli, brussels sprouts and cauliflower, patients were asked the frequency of their consumption using 10 predefined categories of intake, ranging from "never" to "2+ times per day", as well as their portion sizes, from "less than ¼ cup" to "more than 1 cup". The FFQ has been previously validated using 2 subsequent, 24-hour recalls in a subset of the cohort [7, 23, 24].

Cancer ascertainment

Cases of incident bladder cancer were identified through December 31, 2011, through linkage of the NIH-AARP cohort database the 8 state cancer registry databases and the National Death Index Plus. The registries are certified to have >90% case ascertainment within 24 months of cancer diagnosis by the North American Association of Central Cancer Registries. Participants were tracked annually by matching with the National Change of Address database and through processing of undeliverable mail by the U.S. Postal Service, and through direct responses from participants and other address update services. Deaths from bladder cancer was ascertained through December 30, 2011 by linkage with the National Death Index Plus and the Social Security Administration death master file [25-27].

Statistical analysis

We first examined the normality of all variables. Descriptive statistics were presented using Mean ± SD. Anthropometric parameters were compared among the quintiles using Student's t-test, Wilcoxon Signed Rank, or Chi-Square as appropriate. Within each quintile, univariate and multivariate Cox-proportional hazard models were performed. Hazard ratios were displayed with 95% Confidence Interval for different types of bladder cancers, adjusted by marital status, education levels, race, sex, body mass index (BMI), entry age, history of smoking and any first-degree relatives with cancer, and dietary-related variables specifically food energy, total meat consumption, and daily fiber (CSFII) from vegetables. All statistical tests were two-sided and p-values < 0.05 were considered significant. Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Cohort description

Our cohort included 515,628 individuals (312,461 men and 203,167 women). The cohort reported consuming 0.27 ± 0.34 servings of cruciferous vegetables per day. 8257 reported no consumption. Age, marital status, race, and income were similar across quintiles of cruciferous vegetables. Similarly, BMI, smoking status, and level of physical activity was similar across groups (**Table 1**).

Bladder cancer incidence and cruciferous vegetable consumption

A total of 8,567 cases of incident bladder were identified with 7,313 (85.4%) in men and 1,254 (14.6%) in women) during 15 years of follow up (**Table 2**). In situ carcinoma accounted for 2,610 (30.5%) of cases, localized carcinoma for 2,259 (26.4%) of cases, low grade carcinoma for 3,907 (45.6%) of cases, high grade carcinoma for 3,264 (38.1%) of cases, advanced carcinoma for 439 (5.12%) and fatal carcinoma for 1,233 (14.4%) of cases. It is important to note that one individual diagnosis may be overlapping in several bladder cancer sub categories (for example, the cancer was both low grade and in situ). We found no significant associations between cruciferous vegetable consumption and bladder cancer. Specifically, there was no trend for bladder cancer incidence across quintiles from very low to high cruciferous vegetable consumption. While confidence intervals for individual quintiles in bladder cancer subsets suggest significant associations, the absence of a dose-response relationship is shown in the non-significant p-values across the quintiles arguing against biological effects. In addition, no associations were seen when examining individual cruciferous vegetables or by bladder cancer type (**Table 2**).

Smoking history, bladder cancer risk and cruciferous vegetable consumption

Given the association between smoking and bladder cancer, we performed a stratified analysis based on smoking status to determine if the association between cruciferous vegetable consumption and incident bladder cancer changed. For all categories of smoking status, there was no association between cruciferous vegetable consumption and bladder cancer (**Table 3**).

Discussion

Our report represents the largest analysis of cruciferous vegetable consumption and incident bladder cancer to date. We found no significant relationship between cruciferous vegetable consumption and risk of bladder cancer, regardless of the type of vegetable (broccoli, brussels sprouts and cauliflower, or composite) and across all grades and stages of bladder cancer including: in situ, localized, low grade, high grade, and fatal cancer. While several analyses reached statistical significance, the lack of a consistent dose-dependent association argues against a biological explanation. Findings were similar for both men and women, and after stratifying by smoking status.

Prior to our study, evidence from epidemiological studies had been mixed. A small cohort study examining the intake of cruciferous vegetables in 239 patients with bladder cancer showed an inverse relationship between bladder cancer mortality and increased broccoli intake [15]. Another small case-control study similarly found an inverse relationship between the risk of bladder cancer and consumption of cruciferous vegetables [14]. Meta analyses performed across several studies-including prospective cohort and case-control studies-support that cruciferous vegetables are associated with a decreased risk for bladder cancer [9, 19, 20]. However, these studies were limited by the relatively small number of cases in each study and the limited number of studies available to be included in the meta-analyses. The most recent meta-analysis across 5 cohort and 5 case control studies, totaling in 5,772 individuals, reported a significantly decreased risk of incident bladder cancer in association with cruciferous vegetable intake [19]. However, the decrease in risk was found to be significant

Table 1. Baseline characteristics of people with bladder cancer in the NIH-AARP diet and health study

Total Participants: 515,628	Quintiles of Total Cruciferous Vegetables Intake				
	1	2	3	4	5
By quintile n (%)	112,853 (21.9)	96,858 (18.8)	99,356 (19.3)	103,921 (20.2)	102,640 (19.9)
Gender n (%)					
Female	36,209 (17.8)	35,931 (17.7)	39,624 (19.6)	43,773 (21.6)	47,630 (23.4)
Male	76,644 (24.5)	60,927 (19.5)	59,732 (19.1)	60,148 (19.3)	55,010 (17.6)
Age mean ± SD	62 ± 5	62 ± 6	62 ± 5	62 ± 5	62 ± 5
Age at 1/1/1985 mean ± SD	50 ± 6	50 ± 5	50 ± 5	50 ± 5	50 ± 5
BMI mean ± SD	27.2 ± 5.0	27.2 ± 5.0	27.1 ± 5.0	27.1 ± 5.1	27.1 ± 5.4
BMI n (%)					
Below Normal	1,223 (24.5)	884 (17.7)	860 (17.2)	988 (19.8)	1,046 (20.9)
Normal Weight	35,134 (20.9)	30,958 (18.4)	32,675 (19.4)	34,743 (20.6)	34,884 (20.7)
Overweight	49,207 (22.5)	41,946 (19.2)	42,405 (19.4)	43,588 (20.0)	41,184 (18.9)
Obese	22,233 (21.9)	19,245 (18.9)	19,460 (19.2)	20,247 (19.9)	20,348 (20.0)
Severely Obese	1,935 (20.0)	1,673 (17.3)	1,763 (18.2)	1,967 (20.3)	2,359 (24.3)
Birth Cohort n (%)					
1925-1930	38,342 (22.5)	32,387 (18.9)	32,447 (18.9)	34,666 (20.2)	33,481 (19.5)
1931-1935	31,301 (21.2)	27,897 (18.9)	28,723 (19.5)	29,868 (20.3)	29,736 (20.2)
1936-1940	25,687 (21.4)	22,511 (18.8)	23,291 (19.4)	24,277 (20.2)	24,158 (20.1)
1941-1945	17,523 (22.8)	14,063 (18.3)	14,895 (19.4)	15,110 (19.7)	15,265 (19.9)
Marital Status n (%)					
Married	77,559 (21.8)	68,488 (19.2)	70,660 (19.8)	73,151 (20.5)	66,754 (18.7)
Widowed	11,663 (21.2)	9,967 (18.1)	10,190 (18.5)	11,030 (20.0)	12,307 (22.3)
Divorced	15,223 (22.0)	12,482 (18.0)	12,576 (18.1)	13,175 (19.0)	15,876 (22.9).
Separated	1,426 (23.5)	1,077 (17.7)	1,052 (17.3)	1,127 (18.6)	1,390 (22.9).
Never Married	5,595 (23.2)	4,167 (17.3)	4,230 (17.5)	4,723 (19.6)	5,413 (22.4)
Education n (%)					
< 12 years	9,428 (28.7)	6,243 (19.0)	5,588 (17.0)	5,725 (17.4)	5,861 (17.8)
High school/ Some College	63,180 (23.3)	52,358 (19.3)	51,417 (19.0)	53,248 (19.6)	50,869 (18.8)
Completed college or more	36,345 (18.5)	35,641 (18.2)	39,717 (20.2)	42,118 (21.5)	42,478 (21.6)
Race n (%)					
Non-Hispanic White	102,786 (21.9)	89,526 (19.1)	91,747 (19.5)	95,453 (20.3)	90,075 (19.2)
Non-Hispanic Black	3,143 (15.5)	3,305 (16.2)	3,443 (16.9)	4,044 (19.9)	6,410 (31.5)
Hispanic	3,376 (34.0)	1,622 (16.3)	1,565 (15.8)	1,479 (14.9)	1,897 (19.1)
Asian/Pacific Islander	995 (15.5)	913 (14.2)	1,147 (17.8)	1,318 (20.5)	2,069 (32.1)
Pacific Islander	115 (18.1)	108 (17.0)	106 (16.7)	114 (18.0)	191 (30.1)
American Indian/Alaskan Native	350 (23.3)	266 (17.7)	224 (14.9)	283 (18.9)	377 (25.1)
Unknown	2,088 (29.1)	1,118 (15.6)	1,124 (15.7)	1,230 (17.1)	1,621 (22.6)
Median Household Income (dollars)	47,328	48,071	49,265	48,992	48,664
Smoking status n (%)					
Never	36,925 (20.5)	32,342 (18.0)	35,283 (20.0)	37,723 (21.0)	37,842 (21.0).
Former	53,826 (21.2)	48,458 (19.2)	49,159 (19.4)	51,325 (20.3)	50,337 (20.0)
Current	17,075 (27.4)	12,548 (20.2)	11,282 (18.1)	11,138 (17.9)	10,211 (16.4)
Physical activity n (%)					
< 3 time/month	45,047 (27.5)	33,199 (20.3)	30,750 (18.8)	29,009 (17.7)	25,753 (15.7)
1-2 times/week	22,969 (20.8)	21,481 (19.5)	22,318 (20.2)	23,058 (20.9)	20,418 (18.5)
3-4 times/week	25,057 (18.3)	24,868 (18.2)	27,172 (19.9)	29,691 (21.7)	29,829 (21.8)
≥ 5 times/week	17,892 (18.1)	16,353 (16.5)	18,219 (18.4)	21,190 (21.4)	25,397 (25.6)
Other Dietary Factors mean ± SD					
Food energy (kcal)	1,666 ± 941	1,729 ± 816	1,836 ± 834	1,941 ± 860	2,247 ± 1345
Daily fiber from vegetables (g/day)	3.8 ± 2.7	4.7 ± 2.5	5.7 ± 2.6	7.1 ± 2.9	11.5 ± 7.1
Total meat (g/day)	109 ± 96	116 ± 80	126 ± 109	136 ± 90	157 ± 162

Abbreviations: n: number; SD: Standard Deviation; kcal: kilocalories; g: grams.

Table 2. Hazard ratio for bladder cancer in relation to consumption of cruciferous vegetables stratified by quintile of reported consumption

		Broccoli		Cauliflower/Brussel Sprouts		Composite/Total Cruciferous	
		n	Fully Adjusted HR (CI)	n	Fully Adjusted HR (CI)	n	Fully Adjusted HR (CI)
All Bladder Cancer	Quintile 1	2,081	ref	1,920	ref	2,016	ref
	Quintile 2	1,362	0.991 (0.920, 1.066)	1,478	1.007 (0.936, 1.084)	1,714	1.022 (0.953, 1.095)
	Quintile 3	1,933	1.007 (0.941, 1.077)	1,800	1.003 (0.936, 1.076)	1,613	0.986 (0.917, 1.060)
	Quintile 4	2,058	1.024 (0.956, 1.097)	1,756	1.019 (0.949, 1.094)	1,667	1.021 (0.949, 1.100)
	Quintile 5	1,133	1.083 (0.989, 1.185)	1,613	1.064 (0.984, 1.149)	1,557	1.082 (0.990, 1.182)
	p trend (*p* value)		0.214		0.479		0.262
High Grade Bladder Carcinoma	Quintile 1	798	ref	770	ref	785	ref
	Quintile 2	543	1.026 (0.911, 1.154)	545	0.927 (0.824, 1.042)	679	1.066 (0.953, 1.191)
	Quintile 3	739	1.025 (0.919, 1.144)	707	0.97 (0.868, 1.085)	589	0.955 (0.849, 1.074)
	Quintile 4	789	1.037 (0.927, 1.160)	620	0.911 (0.811, 1.023)	615	1.002 (0.887, 1.131)
	Quintile 5	395	1.068 (0.920, 1.239)	622	1.053 (0.930, 1.193)	596	1.184 (1.025, 1.367)
	p trend (*p* value)		0.754		0.550		0.224
Low Grade Bladder Carcinoma	Quintile 1	946	ref	844	ref	898	ref
	Quintile 2	601	0.974 (0.873, 1.088)	683	1.045 (0.937, 1.165)	854	0.99 (0.891, 1.099)
	Quintile 3	884	0.993 (0.898, 1.098)	811	1.03 (0.928, 1.144)	762	1.028 (0.925, 1.143)
	Quintile 4	929	1.01 (0.913, 1.119)	852	1.105 (0.995, 1.226)	787	1.05 (0.943, 1.170)
	Quintile 5	547	1.04 (0.912, 1.187)	717	1.029 (0.916, 1.155)	706	0.995 (0.874, 1.133)
	p trend (*p* value)		0.729		0.762		0.754
Fatal Bladder Carcinoma	Quintile 1	333	ref	279	ref	314	ref
	Quintile 2	195	0.877 (0.724, 1.064)	207	1.002 (0.826, 1.216)	241	0.95 (0.791, 1.141)
	Quintile 3	268	0.873 (0.731, 1.043)	283	1.076 (0.897, 1.291)	220	0.901 (0.744, 1.092)
	Quintile 4	279	0.893 (0.745, 1.071)	226	0.911 (0.750, 1.107)	237	0.984 (0.809, 1.197)
	Quintile 5	158	1.023 (0.808, 1.296)	238	1.146 (0.934, 1.406)	221	1.103 (0.873, 1.394)
	p trend (*p* value)		0.599		0.874		0.896
Localized Bladder Carcinoma	Quintile 1	594	ref	553	ref	554	ref
	Quintile 2	372	0.992 (0.863, 1.141)	377	0.85 (0.738, 0.979)	460	1.056 (0.924, 1.206)
	Quintile 3	481	0.911 (0.798, 1.040)	453	0.873 (0.763, 0.998)	398	0.913 (0.791, 1.053)
	Quintile 4	534	0.995 (0.872, 1.136)	442	0.888 (0.774, 1.018)	407	0.985 (0.851, 1.140)
	Quintile 5	278	0.998 (0.836, 1.191)	434	1.023 (0.883, 1.184)	440	1.234 (1.041, 1.462)
	p trend (*p* value)		0.491		0.491		0.059

Advanced Bladder Carcinoma	Quintile 1	105	ref	113	ref	105	ref
	Quintile 2	87	1.423 (1.044, 1.941)	63	0.743 (0.534, 1.034)	97	1.157 (0.858, 1.560)
	Quintile 3	92	1.1 (0.807, 1.500)	96	0.973 (0.726, 1.303)	71	0.943 (0.681, 1.307)
	Quintile 4	103	1.233 (0.903, 1.682)	87	0.932 (0.688, 1.262)	97	1.251 (0.912, 1.715)
	Quintile 5	52	1.282 (0.854, 1.925)	80	0.93 (0.663, 1.306)	69	1.07 (0.718, 1.594)
	p trend (*p* value)		0.634		0.620		0.785
In Situ Bladder Carcinoma	Quintile 1	646	ref	573	ref	593	ref
	Quintile 2	403	0.976 (0.854, 0.115)	466	1.043 (0.915, 1.189)	540	1.067 (0.941, 1.210)
	Quintile 3	599	1.02 (0.903, 1.151)	542	0.983 (0.866, 1.116)	501	1.031 (0.906, 1.174)
	Quintile 4	603	0.968 (0.854, 1.098)	553	1.052 (0.926, 1.195)	512	1.035 (0.906, 1.184)
	Quintile 5	359	1.125 (0.958, 1.322)	476	1.007 (0.874, 1.161)	464	1.04 (0.886, 1.222)
	p trend (*p* value)		0.271		0.722		0.764

Abbreviations: n: number; HR: Hazard Ratio; CI: Confidence Interval; ref: reference.

Table 3. Risk of Bladder Cancer by smoking status across quintiles of cruciferous vegetable consumption

		Broccoli		Cauliflower/Brussel Sprouts		Composite/Total Cruciferous	
		n	Fully Adjusted HR (CI)	n	Fully Adjusted HR (CI)	n	Fully Adjusted HR (CI)
Never Smokers	Quintile 1	32,680	ref	38,345	ref	36,925	ref
	Quintile 2	27,922	0.998 (0.833, 1.197)	31,542	1.010 (0.848, 1.203)	32,342	0.968 (0.817, 1.146)
	Quintile 3	42,096	1.024 (0.868, 1.207)	38,811	1.048 (0.888, 1.238)	35,283	0.943 (0.795, 1.119)
	Quintile 4	47,274	1.010 (0.857, 1.191)	35,174	1.090 (0.920, 1.292)	37,723	0.949 (0.797, 1.132)
	Quintile 5	30,143	1.086 (0.880, 1.341)	36,243	1.164 (0.970, 1.397)	37,842	1.102 (0.898, 1.353)
	p trend (*p* value)		0.663		0.493		0.421
Former Smokers	Quintile 1	51,745	ref	52,507	ref	53,826	ref
	Quintile 2	39,951	0.941 (0.856, 1.035)	43,404	1.013 (0.924, 1.111)	48,458	1.014 (0.928, 1.108)
	Quintile 3	59,398	1.013 (0.930, 1.103)	54,076	0.981 (0.898, 1.072)	49,159	0.989 (0.903, 1.084)
	Quintile 4	62,732	1.037 (0.951, 1.131)	51,935	1.013 (0.927, 1.108)	51,325	1.019 (0.928, 1.119)
	Quintile 5	39,279	1.054 (0.941, 1.181)	51,183	1.029 (0.933, 1.135)	50,337	1.069 (0.956, 1.195)
	p trend (*p* value)		0.444		0.670		0.599
Current Smokers	Quintile 1	16,527	ref	15,667	ref	17,075	ref
	Quintile 2	11,332	1.134 (0.972, 1.323)	10,714	0.982 (0.834, 1.156)	12,548	1.087 (0.934, 1.266)
	Quintile 3	14,905	0.958 (0.822, 1.117)	12,828	1.037 (0.888, 1.212)	11,282	1.003 (0.851, 1.182)
	Quintile 4	12,135	0.972 (0.824, 1.145)	11,911	0.969 (0.823, 1.140)	11,138	1.095 (0.925, 1.296)
	Quintile 5	7,355	1.203 (0.970, 1.491)	11,134	1.089 (0.909, 1.303)	10,211	1.088 (0.882, 1.343)
	p trend (*p* value)		0.261		0.851		0.408

Abbreviations: n: number; HR: Hazard Ratio; CI: Confidence Interval; ref: reference.

only in the case control studies, but not the cohort studies.

Conversely, several other studies showed no association between risk of bladder cancer and cruciferous vegetable consumption [9]. These include a prospective study examining cruciferous vegetables intake and bladder cancer risk in smokers, a prospective population based cohort study of 82,000 people, and a meta-analysis of fruits and vegetables intake [9, 21, 22, 28].

Our study, the largest to date, also showed no relationship between cruciferous vegetable intake and bladder cancer. The major strength of our study is its large size, including over 500,000 participants from diverse areas across the United States. The size of the study population allows detection of association between specific vegetables and Cruciferae broadly if any relationships truly exist with bladder cancer with a high degree of certainty. The large size also allowed for assessments of associations across bladder cancer subtypes, which no previous study has had the power to detect. Our large population and data collection also allowed us to assess whether the effects of cruciferous vegetables was modified by smoking status. Since sulforaphane, a bioactive micronutrient found at high levels in Cruciferae induces enzymes that reduce and inactivate carcinogens [11-13], stratification for smoking status could unveil potential associations. However, smoking status did not modify the lack of association between dietary cruciferous vegetable consumption and bladder cancer. Finally, our study was also a prospective cohort study, which minimizes the risk of recall bias, a common problem in previous dietary assessment studies.

It is important to note that there was a strong scientific rationale for the hypothesis that cruciferous vegetables may offer protection against bladder cancer. Several in vitro and in vivo experimental studies have looked at the potential anticancer properties of cruciferous vegetables. The leading hypothesis was that isothiocyanates-a uniquely abundant metabolite found in cruciferous vegetables-is the bioactive compound responsible for anticancer activity. In vitro studies have found that isothiocyanates can induce apoptosis and cell cycle arrest in human bladder cancer cells [16, 18]. In vivo studies have also supported this hypothesis, with long term rat studies showing decrease in incidence and progression of bladder cancer in rats fed with both broccoli sprout extracts, and other studies finding that broccoli isothiocyanates can inhibit established bladder cancer in xenograft tumor models [16-18]. Isothiocyanates' proposed mechanism of action include: modulation of carcinogen metabolizing enzymes, cell cycle apoptosis, and epigenetic modulation [9, 11].

There are several explanations for the conflicting results of preclinical in vitro and vivo experiments and our large-scale human study. In the in vitro and in vivo studies, isothiocyanates or vegetable extracts are delivered directly to cells or animals in their pure form and in a controlled manner. In contrast, epidemiological studies cannot elucidate to this detail of consumption, and we cannot be certain if the quantities of cruciferous vegetables consumed translates to therapeutic concentrations of isothiocyanates, especially after considering bioavailability and metabolism. In addition, Abbaoui et al also note how cruciferous vegetables are consumed can significantly change the amount of isothiocyonates and other bioactives an individual is exposed to [9]. For example, quantities of isothiocyanates in vegetables are significantly reduced by cooking and storage processes [29-31]. Therefore, the amount of isothiocyanates an individual consumes through cruciferous vegetables may not be enough to ever reach therapeutic levels to protect against bladder cancer.

Our study included several noteworthy limitations. First, dietary information was collected at a single point in time and would not capture changes in diet over time. Therefore, we could not assess how cumulative and longitudinal consumption of cruciferous vegetables affect bladder cancer risk. Second, nearly all dietary assessment studies include the possibility of reporting error, where the reported amount of consumption by the individual is not accurate. Third, considering the latency period of bladder cancer, our follow up time of 15 years may not have been sufficient to fully capture an association as some bladder cancer cases may have not yet had time to manifest or be diagnosed. Still, if a meaningful protective effect exists, one would expect to see some suggestion of an association by 15 years. Fourth, there remains the possibility that some cases of bladder cancer were undiagnosed, impacting their inclusion in our data analyses. However, we do not expect this to affect our data analysis and subsequent results dramatically as the number cases included in our data analysis was quite large.

In summary, contrary to preclinical data and some smaller studies in humans, our analysis showed that increasing consumption of cruciferous vegetables is not associated with reduced risk of bladder cancer. We encourage patients to consume cruciferous vegetables for their other health benefits, especially for cardiovascular health; however, they should not expect this diet to reduce their risk for bladder cancer.

Conclusion

Based on the current analysis, intake of cruciferous vegetables is not associated with bladder cancer risk.

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Disclosure of conflict of interest

None.

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