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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Intake of Cruciferous Vegetables Modifies Bladder Cancer Survival

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Abstract

Background: Intake of cruciferous vegetables, a rich source of dietary isothiocyanates, has been inversely associated with risk of bladder cancer. Due to the potent antiproliferative effects of dietary isothiocyanates on bladder cancer in *in vitro* and *in vivo* models, cruciferous vegetable intake may also play a role in survival among patients with bladder cancer.

Methods: Using information obtained from the Roswell Park Cancer Institute Tumor Registry, patient medical records, and routinely collected questionnaire data, we examined potential associations between intake of cruciferous vegetables and survival among bladder cancer patients. As cooking can substantially reduce or destroy isothiocyanates, consumption of raw versus cooked cruciferous vegetables was examined separately. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazard models.

Results: A total of 239 bladder cancer patients were included in the study. After an average of 8 years of follow-up, 179 deaths occurred, with 101 deaths attributable to bladder cancer. After adjustment for other prognostic factors, a strong and significant inverse association was observed between bladder cancer mortality and broccoli intake, in particular raw broccoli intake (≥1 versus <1 serving per month; HR for overall death, 0.57; 95% CI, 0.39-0.83; HR for disease-specific death, 0.43; 95% CI, 0.25-0.74). There were no significant associations for total vegetables, total fruits, or other individual cruciferous vegetables.

Conclusions: Considering the strong preclinical evidence, intake of broccoli may improve bladder cancer survival.

Impact: Further prospective investigation is warranted to confirm the potential role of cruciferous vegetables in bladder cancer prognosis. *Cancer Epidemiol Biomarkers Prev; 19(7); 1806–11. ©2010 AACR.*

Introduction

A challenge exists in the management of bladder cancer. Unlike many other cancers, the majority of bladder cancers (~75%) are diagnosed early as superficial disease with tumors confined to the mucosa or submucosa. However, the cancer typically recurs (approximately 50-70%), and some patients further experience disease progression to a muscle-invasive stage with worse prognosis (1-3). Currently, several therapeutic agents are offered intravesically to high-risk patients to inhibit disease recurrence and progression. However, the cost of multiple use of clinical resources, frequent local side effects, and controversial long-term effects are all of concern (4, 5). Studies on promising dietary components may offer a new strategy for improvement of bladder cancer prognosis.

Intake of cruciferous vegetables has been associated with reduced risk of primary bladder cancer (6-9), which is believed to be at least partly attributed to the high content of glucosinolates, the precursors of isothiocyanates and indole-3-carbinol in cruciferous vegetables (10). Dietary isothiocyanates are a family of promising cancer chemopreventive agents with multifaceted anticancer mechanisms, including the induction of carcinogen-detoxification phase 2 enzymes, arrest of cell cycle progression, and induction of apoptosis. The potent antiproliferative activity of dietary isothiocyanates has been observed in a panel of cultured human bladder cancer cells that represent low-grade superficial, high-grade invasive, as well as doxorubicin-resistant bladder cancer (11-14). More importantly, urinary metabolites of isothiocyanates elicited the same anticancer response as their parent compounds in human bladder cancer cells, supporting the plausibility for a role of dietary isothiocyanates and/or isothiocyanate-rich cruciferous vegetables in bladder cancer prognosis. In an *in vivo* rat model in which *N*-butyl-*N*(4-hydroxybutyl)-nitrosamine was used to induce bladder carcinogenesis, orally ingested isothiocyanates in broccoli sprout extracts were rapidly

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and almost exclusively excreted into the bladder and significantly inhibited bladder tumor formation by 61% (15). Recently, in a rat orthotopic bladder cancer model, our group was able to show the inhibition of bladder cancer development and progression by low oral doses of allyl isothiocyanate (the isothiocyanate rich in mustard and horseradish). This activity seems to be bladder cancer–specific, as no effect was observed on the development of subcutaneous cancer at such low dose levels (16). Accordingly, two to three orders of magnitude higher concentration of isothiocyanate and their corresponding metabolites was found in the urine than in the plasma. This selectivity renders the bladder an ideal target for isothiocyanate as well as isothiocyanate-rich cruciferous vegetables. The rat orthotopic bladder cancer model resembles human bladder cancer development both in histology and behavior, and has been used to test therapeutic agents for bladder cancer treatment (17, 18). Therefore, these results provide preclinical evidence to support the potential role of isothiocyanate-rich cruciferous vegetables in bladder cancer prognosis. We applied this model to humans by examining associations between

Table 1. Baseline characteristics of bladder cancer patients (n = 239) by survival status, RPCI

Characteristic	No. of participants	Overall death		Death from bladder cancer	
		No. of events	Crude HR (95% CI)	No. of events	Crude HR (95% CI)
Age at diagnosis, y					
<60	75	46		32	
60-70	103	77	1.41 (0.98-2.04)	46	1.11 (0.71-1.75)
>70	61	56	1.99 (1.34-2.96)	23	1.03 (0.60-1.76)
SEER stage*					
Localized	130	83		30	
Advanced	108	95	2.04 (1.51-2.74)	71	3.90 (2.54-5.99)
Tumor grade†					
I	84	58		29	
II	112	86	1.62 (1.18-2.32)	53	1.24 (0.70-2.22)
Unspecified	43	35	1.18 (0.78-1.80)	19	1.73 (1.10-2.72)
Surgery type					
TURBT	154	120		64	
Cystectomy	66	55	1.56 (1.13-2.15)	36	1.71 (1.13-2.57)
Unspecified	19	4	0.53 (0.20-1.45)	1	0.20 (0.03-1.47)
Radiation therapy					
No	191	132		67	
Yes	48	47	1.93 (1.38-2.70)	34	2.53 (1.67-3.83)
Chemotherapy					
No	101	64		25	
Yes	138	115	1.28 (0.95-1.74)	76	2.15 (1.37-3.39)
Immunotherapy					
No	187	139		80	
Yes	52	40	0.79 (0.56-1.13)	21	0.73 (0.45-1.18)
Smoking status					
Never	47	28		10	
Former	136	107	1.65 (1.09-2.50)	63	2.57 (1.32-5.02)
Current	56	44	1.77 (1.10-2.85)	28	2.75 (1.33-5.66)
Gender					
Male	186	144		84	
Female	53	35	0.55 (0.38-0.80)	17	0.54 (0.32-0.91)
Year of admission					
≤1990	132	106		53	
>1990	107	73	1.01 (0.74-1.36)	48	1.19 (0.80-1.76)

Abbreviations: SEER, Surveillance Epidemiology and End Results; TURBT, transurethral resection of bladder tumor.

*Surveillance Epidemiology and End Results stage: Localized tumor included tumors *in situ* or confined to the bladder; Advanced tumor included tumors spreading regionally or distantly.

†Tumor grade: Grade I tumor included well- or moderately differentiated tumors; grade II tumor included poor or undifferentiated tumors.

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Table 2. Bladder cancer survival by fruit and vegetable intake, RPCI

	No. of participants	Overall death		Death from bladder cancer	
		No. of events	Adjusted HR* (95% CI)	No. of events	Adjusted HR* (95% CI)
Fruits, servings/mo					
<27.5	81	59		30	
27.5-51	82	59	0.86 (0.59-1.24)	34	0.94 (0.57-1.55)
>51	76	61	0.91 (0.62-1.33)	37	1.09 (0.66-1.81)
Vegetables, servings/mo					
<52	83	60		32	
52-85.5	80	61	0.90 (0.62-1.30)	36	0.95 (0.59-1.55)
>85.5	76	58	0.91 (0.62-1.36)	33	1.06 (0.63-1.78)
Cruciferous, servings/mo					
<5.5	76	58		31	
5.5-14	80	59	0.96 (0.67-1.39)	37	1.05 (0.65-1.71)
>14	83	62	0.87 (0.60-1.26)	33	0.89 (0.53-1.48)
Raw cruciferous, servings/mo					
<1	66	56		32	
1-3	99	68	0.67 (0.46-0.97)	39	0.67 (0.41-1.10)
>3	74	55	0.73 (0.50-1.06)	30	0.73 (0.44-1.21)

*Adjusted for age at diagnosis (continuous), total meat intake (continuous), pack-years of smoking (continuous), tumor stage (localized or advanced), and radiation therapy (yes or no).

consumption of cruciferous vegetables as measured by a food frequency questionnaire among patients with bladder cancer at the Roswell Park Cancer Institute (RPCI), and disease-free survival and overall survival.

Materials and Methods

The study population included 239 patients diagnosed with primary bladder cancer at RPCI between 1980 and 1998, who completed a comprehensive epidemiologic questionnaire. A detailed description of the study population and the epidemiologic data collection has been previously published (7). Briefly, a 44-item food frequency questionnaire was used to assess usual diet in the few years before diagnosis and queried intake of fruits and vegetables, cruciferous vegetables, and foods that are rich sources of vitamins A, C, and E, and fiber (19). Four food categories (fruits, vegetables, cruciferous vegetables, and raw cruciferous vegetables) were created by combining monthly frequency of use of each food item under the categories. The cruciferous vegetable category consisted of broccoli (raw and cooked), cabbage (raw and cooked), cauliflower (raw and cooked), Brussels sprouts, and greens including kale, turnip, collard, and mustard greens. The raw cruciferous vegetable consumption category, defined as raw broccoli, raw cabbage, and raw cauliflower, was created to more accurately represent dietary intake of isothiocyanates, as it is known that cooking substantially reduces isothiocyanate yield from cruciferous vegetables (20, 21). Intake of each food category was divided into tertiles, whereas for individual cruciferous vegetables, intake was divided into two categories (<1 or ≥1 servings per month). For each vegetable, a serving was defined to be equal to one-half cup.

Clinical information on tumor stage, grade, treatment, and survival was abstracted from the RPCI tumor registry, and medical records were reviewed to collect missing information. The two prognostic outcomes considered were as follows: overall death and death from bladder cancer. Overall death included death from any cause including bladder cancer. Death from bladder cancer included death attributable to bladder cancer as a primary or underlying cause on the death certificate. A total of 16 patients with unclear cause of death were included in the analysis of overall death but excluded from the analysis of death from bladder cancer. Disease recurrence was not included as an outcome in the current analysis due to incomplete information for majority of the patients. The conduct of the study was approved by the RPCI Institutional Review Board.

Survival time was calculated in months from date of diagnosis to date of death, loss to follow-up, or date of last contact (July 2007). Kaplan-Meier estimates of survival were generated, and a log-rank test was used to test the differences by each variable. For multivariable analysis, Cox proportional hazard regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI). A set of potential confounders including age at diagnosis, tumor stage, grade, surgery, radiation, chemotherapy, immunotherapy, year of admission, gender, and smoking status was considered for inclusion in adjusted models using a forward selection technique. Patients were predominantly Caucasian (98%); therefore,

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race was not included as a potential confounder. As smoking is a major risk factor for bladder cancer, we included pack-years in the model, computed as the number of packs of cigarettes smoked per day times the number of years smoked. Total meat intake was also considered in the model to partially adjust for differences in dietary patterns associated with vegetable intake. The final model included covariates that were statistically significant ($P < 0.05$) when entered into the model individually. The proportional hazard assumption was confirmed for all covariates. All statistical analyses were conducted using SAS for Windows, version 9.1.

Results

Of the 239 patients evaluated, 179 deaths (74.9%) were ascertained through July 2007. Mean follow-up time was 96 months (median, 77; range 1-301 mo). Among the 179 deaths, 101 (56.4%) were attributable to bladder cancer. Kaplan-Meier curves for overall survival and bladder cancer–specific survival are provided in Supplementary Figs. S1 and S2, respectively. As shown in Table 1, age at diagnosis, Surveillance Epidemiology and End Results stage, tumor grade, smoking status, gender, and treatment including surgery type, radiation, and chemotherapy were significantly associated with survival. However, only age at diagnosis, stage, smoking status, and radiation therapy remained significant in the multivariate models, indicating their independent prognostic roles in bladder cancer survival. Radiation therapy was associated with worse survival, likely due to the selection of patients with more advanced disease. Survival did not differ significantly by year of admission.

We observed no associations between intake of total fruits, total vegetables, or total cruciferous vegetables and bladder cancer survival (Table 2). However, higher consumption of raw cruciferous vegetables was associated with a 33% reduction in overall mortality (HR, 0.67; 95% CI, 0.46-0.97), but not for disease-specific death.

With regard to intake of individual cruciferous vegetables, we observed notable reductions in bladder cancer mortality with higher consumption of broccoli, particularly raw broccoli (survival curve is provided in Supplementary Fig. S3; Table 3). After adjustment for age at diagnosis, tumor stage, grade, pack-years of smoking, and total meat intake, higher consumption of raw broccoli was associated with a >2-fold reduction in risk of disease-specific death (HR, 0.43; 95% CI, 0.25-0.74), as well as reduction of

Table 3. Bladder cancer survival by individual cruciferous vegetable intake, RPCI

	No. of participants	Overall death		Death from bladder cancer	
		No. of events	Adjusted HR* (95% CI)	No. of events	Adjusted HR* (95% CI)
Broccoli raw, servings/mo					
<1	184	142		85	
≥1 (mean, 3.9)	55	37	0.57 (0.39-0.83)	16	0.43 (0.25-0.74)
Broccoli cooked, servings/mo					
<1	96	78		44	
≥1 (mean, 5.1)	143	101	0.67 (0.49-0.91)	57	0.68 (0.45-1.01)
Cabbage raw, servings/mo					
<1	128	94		54	
≥1 (mean, 4.1)	111	85	1.08 (0.79-1.46)	47	1.11 (0.74-1.66)
Cabbage cooked, servings/mo					
<1	155	114		66	
≥1 (mean, 4.1)	84	65	1.07 (0.77-1.48)	35	1.15 (0.75-1.77)
Cauliflower raw, servings/mo					
<1	182	140		80	
≥1 (mean, 5.1)	57	39	1.00 (0.69-1.46)	21	1.08 (0.66-1.77)
Cauliflower cooked, servings/mo					
<1	129	99		56	
≥1 (mean, 3.9)	110	80	0.92 (0.68-1.25)	45	0.95 (0.63-1.42)
Brussels sprout, servings/mo					
<1	176	132		73	
≥1 (mean, 4.3)	63	47	1.17 (0.82-1.68)	28	1.37 (0.86-2.18)
Kale, turnip, collard, mustard greens, servings/mo					
<1	194	144		81	
≥1 (mean, 5.1)	45	35	1.15 (0.78-1.69)	20	1.07 (0.63-1.79)

*Adjusted for age at diagnosis (continuous), total meat intake (continuous), pack-years of smoking (continuous), tumor stage (localized or advanced), and radiation therapy (yes or no).

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overall mortality (HR, 0.57; 95% CI, 0.39-0.83). No associations were observed for other individual cruciferous vegetables. We further observed no statistically significant interactions by smoking status or by gender (data not shown).

Discussion

In this study of 239 bladder cancer patients seen at RPCI between 1980 and 1998, survival was not associated with total fruits, total vegetables, or total cruciferous vegetable intake before diagnosis. However, intake of raw cruciferous vegetables was significantly associated with reduced disease-specific (57% reduction) and overall mortality (43% reduction), a result largely driven by raw broccoli intake. The reduction was observed with consumption of at least one serving raw broccoli per month (average intake 3.9 servings/mo), indicating the feasibility of this type of diet intervention strategy. Our findings are consistent with experimental evidence showing that isothiocyanate exposure, as measured by urinary metabolite concentrations, is 3- to 4-fold higher in individuals after consumption of raw compared with cooked broccoli (21). Experimental studies in animals and cell lines indicate that isothiocyanates may be promising chemopreventive agents against bladder cancer (10).

Contrary to the findings observed with broccoli intake, no associations were observed with other individual cruciferous vegetables regardless of whether they were consumed raw or cooked. As usual consumption of individual cruciferous vegetables in the study was similar (means of broccoli, cabbage, and cauliflower consumption were 4.1, 3.9, and 3.3 servings per month, respectively), it is unlikely that this null association was the result of the small range of exposure. It is unclear whether the differential associations observed between individual cruciferous vegetables and bladder cancer survival are related to specific types of isothiocyanates or the amount of isothiocyanates derived from each vegetable. For example, the major isothiocyanate derived from broccoli is sulforaphane, whereas cabbage and cauliflower are abundant in allyl isothiocyanate (22). The two isothiocyanates share the characteristic -N = C = S structure but differ in their side chains, resulting in varied anticancer potencies as well as the underlying mechanisms observed in human bladder cancer cells (12, 13). Investigation of the *in vivo* efficacy of individual isothiocyanates against bladder cancer would offer more clues to understanding these observed associations. Moreover, isothiocyanate yield differs substantially among different cruciferous vegetables due to their wide range of glucosinolate concentration. Jiao et al. (23) showed that total isothiocyanate yield from nine types of cruciferous vegetables in Singapore varied as much as 16-fold. The isothiocyanate content in broccoli was 40% higher than that in cabbage and 2.3-fold higher than that in cauliflower. Furthermore, it is noteworthy that, in addition to isothiocyanates, cruciferous vegetables contain many other compounds with anticancer potential including indoles, vitamins, dietary fiber, and other phytochemicals, which could also contribute to the observed associations either independently and/or in combination with isothiocyanates.

Several limitations need to be taken into consideration in this study. First, questionnaire data, including cruciferous vegetable intake, were collected at the time of diagnosis, which may not represent dietary habits after the disease diagnosis. Cancer survivors are often motivated to modify their diet with the hope of improving prognosis (18). However, such diet modifications tend to be healthy changes such as eating less meat and fat and increasing vegetable and fruit intake (24). Therefore, it is possible that our findings have been underestimated. Validation of the findings in a prospective study using cruciferous vegetable intake after diagnosis would provide more conclusive evidence.

Second, due to the relatively small sample size, we have limited statistical power to examine potential interactions between cruciferous vegetable and other prognostic factors. Cigarette smoking is the strongest risk factor of bladder cancer. Consistent with the potent detoxification effect of isothiocyanates on cigarette-related carcinogens, a strong inverse association was observed between cruciferous vegetable intake and bladder cancer risk among smokers (7). Smoking was an independent prognostic factor for bladder cancer survival in the current study. It is possible that cruciferous vegetable intake may modify the associations between cigarette smoking and bladder cancer survival.

Third, outcome data were collected retrospectively, which could introduce the possibility of misclassification. Moreover, due to the incomplete recurrence data, we were unable to investigate the associations between cruciferous vegetable intake and bladder cancer recurrence, whereas high risk of recurrence is the most common event occurring in bladder cancer patients. Therefore, such information may have a great effect on bladder cancer survivorship.

To our knowledge, this is the first study to investigate the role of cruciferous vegetables in bladder cancer survival. A strong inverse association between broccoli intake and bladder cancer mortality was observed. The strong preclinical evidence of broccoli sprout extract in *in vitro* and *in vivo* bladder cancer models supports the validity of this association. Further large-scale prospective studies are warranted to confirm the potential role of cruciferous vegetables in bladder cancer prognosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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