Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Postdiagnosis Cruciferous Vegetable Consumption and Breast Cancer Outcomes: A Report from the After Breast Cancer Pooling Project

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Abstract

Cruciferous vegetables are a major source of glucosinolate-derived bioactive compounds such as isothiocyanates, which have been shown in animal and *in vitro* studies to inhibit cancer growth and progression. Few studies have investigated cruciferous vegetable intake after diagnosis and breast cancer outcomes. Using data from the After Breast Cancer Pooling Project, which includes prospective data from U.S. and Chinese breast cancer survivors, we evaluated the association of cruciferous vegetables with breast cancer outcomes. Analyses included 11,390 women diagnosed with stage I–III invasive breast cancer (1990–2006) from four cohorts. Cruciferous vegetable intake (g/day) was assessed using food frequency questionnaires (mean of 22 months postdiagnosis). Study heterogeneity was evaluated by the Q statistic; hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using delayed-entry Cox regression models stratified by study. After a median follow-up of 9.0 years, 1,725 deaths and 1,421 recurrences were documented. In pooled analyses using study-specific quartiles, cruciferous vegetable intake was not associated with breast cancer outcomes, adjusting for known clinical prognostic factors and selected lifestyle factors. HRs (95% CIs) by increasing quartiles (reference = lowest quartile) were 1.08 (0.93–1.25), 1.01 (0.87–1.18), and 1.10 (0.95–1.28) for recurrence ($P_{trend} = 0.34$) and 1.01 (0.88–1.15), 0.97 (0.84–1.11), and 0.99 (0.86–1.13) for total mortality ($P_{trend} = 0.84$). No associations were observed for subgroups defined by estrogen receptor status, stage, or tamoxifen therapy. Cruciferous vegetable intake at approximately two years after diagnosis was not associated with recurrence or mortality. Our results do not support an association between postdiagnosis cruciferous vegetable intake and breast cancer outcomes. *Cancer Epidemiol Biomarkers Prev; 22(8); 1451–6. ©2013 AACR.*

Introduction

Cruciferous vegetables, such as cauliflower, cabbage, bok choy, turnip greens, and broccoli, contain high amounts of glucosinolates, which are hydrolyzed to bioactive compounds such as isothiocyanates (ITC) and indoles (1). ITCs are known to induce phase II enzymes, such as glutathione-S-transferases, which are involved in the detoxification of carcinogens (1, 2). Animal and *in vitro* studies have shown that ITCs and indoles can induce apoptosis and cell-cycle arrest, inhibit invasion and migration, and induce antiangiogenesis in cancer cells (1–5). ITCs and indole-3-carbinol have been shown to reduce cell proliferation in human breast cancer cells and inhibit mammary tumor growth *in vivo* (3, 6–8). Some studies have reported an inverse association between higher intakes of cruciferous vegetables and risk of developing breast cancer; however, results are inconsistent (9–12).

To our knowledge, only 2 reports have prospectively evaluated the association between postdiagnosis cruciferous vegetable intake and breast cancer outcomes. One study, a secondary analysis of the Women's Healthy Eating & Living (WHEL) Study, reported an inverse association between baseline higher cruciferous vegetable intake and recurrence among tamoxifen users, but not tamoxifen nonusers (13). However, this study's randomized dietary intervention, which was not stratified by tamoxifen use and achieved a major increase in cruciferous vegetable consumption (14), observed no effect of the intervention on breast cancer recurrence or survival (15). A second cohort study, which did not stratify by tamoxifen use and did not have information on breast cancer recurrence, reported no association between cruciferous intake and breast cancer survival (16).

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Table 1. Select cohort characteristics and cruciferous vegetable intake amount and type, ABCPP ($n = 11,390$)

	WHEL ($n = 1,435$)	LACE ($n = 1,866$)	NHS ($n = 3,902$)	SBCSS ($n = 4,187$)
Age at diagnosis, mean (SD)	51.1 (8.9)	58.6 (10.8)	64.5 (7.6)	53.5 (10.0)
Years of diagnosis, range	1991–2000	1996–2000	1990–2004	2002–2006
Median follow-up, y	11.5	11.8	12.0	5.3
Total deaths, *n*	212	364	641	508
Recurrences, *n*	270	342	402	407
Months between diagnosis and dietary assessment, mean, (range)	23.4 (1.9–48.3)	22.5 (11.0–38.8)	23.8 (0.9–47.9)	18.3 (11.7–34.7)
Cruciferous (g/d) median (10th–90th)	23.8 (6.9–77.9)	22.4 (4.4–74.0)	25.4 (5.6–70.7)	93.0 (39.4–188)
Types of cruciferous vegetables assessed from FFQ	Broccoli, greens (mustard, turnip, collard), cauliflower/Brussels sprouts, watercress, cabbage/coleslaw, radishes, turnips, rutabaga	Broccoli, cooked greens (spinach, mustard greens, turnip greens, collards), cauliflower/cabbage/sauer-kraut/Brussels sprouts, coleslaw	Broccoli, Kale/mustard greens/chard, cauliflower, cabbage/coleslaw, Brussels sprouts	Greens and Chinese greens, cabbage (Chinese cabbage, bok choy, green cabbage), cauliflower, and turnips
Total number of separate items for cruciferous vegetables	8	4	5	5

Given the limited research to date, we used data from the After Breast Cancer Pooling Project (ABCPP), an international collaboration of prospective studies of breast cancer survivors, to investigate the association of cruciferous vegetable intake after diagnosis with breast cancer outcomes.

Materials and Methods

The ABCPP includes pooled data on 18,314 breast cancer survivors from 4 prospective cohorts recruited from U.S. sites and Shanghai, China (17). Three cohorts recruited only patients with breast cancer: the Shanghai Breast Cancer Survival Study (SBCSS; 18), the Life After Cancer Epidemiology (LACE) Study (19), and the WHEL Study (20). The WHEL study was an intervention trial (1995–2006) designed to test adoption of a diet high in vegetables, fruit, and fiber and low in fat among breast cancer survivors. The fourth cohort consists of patients with breast cancer diagnosed in the Nurses' Health Study (NHS; ref. 21). Institutional Review Board approval was obtained for each study, and informed consent was obtained.

Cruciferous vegetable intake was assessed via food frequency questionnaires (FFQ) validated for major nutrients and/or food groups or based on a validated questionnaire. Details on each FFQ have been described (18–22). Vegetable intake was based on FFQs at study enrollment for LACE and WHEL and first postdiagnosis survey for the NHS (Table 1). For the SBCSS, the first postdiagnosis interview was conducted when many patients were receiving chemotherapy/radiotherapy (about 6 months postdiagnosis); therefore the 18-month interview was used. The NHS and LACE study provided data on servings/week, which were converted to grams/day (23).

Outcome ascertainment

Each cohort followed participants to ascertain breast cancer outcomes, including breast cancer recurrence (defined as recurrence/metastasis or development of new primary breast cancer) and mortality outcomes. New primary breast cancers were not available from the NHS. Detailed methods about outcome ascertainment and cohort follow-up have been published (17–21).

Statistical analysis

Women were excluded for the following reasons: breast cancer diagnosis before 1990 ($n = 2,960$), stage IV breast cancer or missing stage ($n = 420$), death or loss to follow-up before dietary assessment ($n = 27$), missing cruciferous vegetable intake ($n = 1,703$), first postdiagnosis dietary measure more than 5 years after diagnosis ($n = 296$), and WHEL study intervention group ($n = 1,537$). The final sample size included 11,390 women. We present pooled results using both study-specific quartiles and common absolute cutpoints [based on estimated servings/day (e.g., half cup of cooked broccoli = 78 g) and adequate sample size].

We used delayed-entry Cox proportional hazards regression models to estimate study-specific HRs and 95% confidence intervals (CI). Entry date was date of enrollment (LACE, WHEL), first postdiagnosis questionnaire (NHS), or 18-month interview (SBCSS). Exit date was date of death (or recurrence/metastasis for the recurrence analysis) or date of last contact (i.e., date of last follow-up survey or last registry linkage, whichever was most recent). The Q statistic was used to test for heterogeneity in risk estimates across studies (24). As *P* values for the Q statistic were not statistically significant, we conducted a pooled analysis using combined data with Cox regression models stratified by study. Covariates, available for all 4 cohorts and selected *a priori*, included age at diagnosis, AJCC 6th edition tumor stage, estrogen receptor (ER)/progesterone receptor (PR) status, cancer treatment (surgery, chemotherapy, radiotherapy, hormonal therapy), education, race/ethnicity, menopausal status, recreational physical activity in metabolic equivalent hours per week (25), smoking, and body mass index (BMI).

Potential effect modifiers included ER status and stage. To compare with the previous WHEL study report, we also evaluated tamoxifen use as a potential effect modifier (13). Multiplicative interactions were tested by using the likelihood ratio test statistic, comparing models with and without the interaction terms. Tests for linear trend were calculated using the median intakes for each quartile and modeling these as continuous variables. The proportional hazards assumption was evaluated by testing the statistical significance of interaction terms for each covariate and survival time. The assumption of proportional hazards was violated for two covariates (stage and ER/PR status); hence, the interaction terms for these covariates with survival time were included in final Cox models, as appropriate. All analyses were conducted using SAS (version 9.3; SAS Institute). Tests of statistical significance were two-sided and *P* values <0.05 were considered statistically significant.

Results

After a median follow-up of 9.0 years, 1,725 deaths and 1,421 recurrences were documented. Table 1 displays select cohort characteristics and amount and types of cruciferous vegetables by cohort. Chinese women consumed the highest amount of cruciferous vegetables (median = 93 g/day); cruciferous vegetable intake was similar by U.S. cohort.

U.S. and Chinese breast cancer survivors who consumed higher amounts of cruciferous vegetables after diagnosis tended to be younger (data not shown). Adjusting for age, higher intake of cruciferous vegetables was associated with both higher education and recreational physical activity levels (among U.S. and Chinese women), whereas current smoking was associated with lower intake of cruciferous vegetables (among U.S. women only), and BMI and clinical characteristics were not associated with cruciferous vegetable intake (data not shown).

Table 2. Multivariable HRs[a] for postdiagnosis cruciferous vegetable intake in association with recurrence and total mortality, ABCPP (n = 11,390)

		Recurrence[b]		Total mortality	
Cruciferous vegetables	**Cohort**	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
Study-specific quartiles (g/d)[c,d]					
Q1	2,833	336	1.00 (Ref.)	454	1.00 (Ref.)
Q2	2,810	357	1.08 (0.93–1.25)	427	1.01 (0.88–1.15)
Q3	2,905	347	1.01 (0.87–1.18)	419	0.97 (0.84–1.11)
Q4	2,842	381	1.10 (0.95–1.28)	425	0.99 (0.86–1.13)
P_{trend}			0.34		0.84
Common cutpoints (g/d)[e]					
<39	5,447	738	1.00 (Ref.)	934	1.00 (Ref.)
39–78	2,806	341	1.00 (0.88–1.15)	378	0.89 (0.79–1.01)
≥78	3,137	342	1.05 (0.89–1.24)	413	1.03 (0.88–1.20)
P_{trend}			0.60		0.82

[a]HRs were from delayed-entry Cox proportional hazards regression models with study as a stratification variable and adjusted for age at diagnosis, ER/PR status, TNM stage, chemotherapy, surgery, radiotherapy, hormonal therapy, smoking, BMI, exercise, menopausal status, race/ethnicity, and education.

[b]566 women were excluded where disease-free follow-up time was ≤date of exposure/enrollment.

[c]Study-specific quartiles were as follows: <10.7, 10.7–22.4, 22.4–43.5, ≥43.5 (LACE); <13.0, 13.0–<23.8, 23.8–44.6, ≥44.6 (WHEL); <15.4, 15.4–25.4, 25.4–43.2, ≥43.2 (NHS); <61.5, 61.5–93, 93–138.0, ≥138.0 (SBCSS).

[d]*P* values for heterogeneity by study were 0.98 and 0.69 for recurrence and total mortality, respectively (using study-specific quartiles). *P* values for heterogeneity by study were 0.89 and 0.91 for recurrence and total mortality, respectively (using common cutpoints).

[e]78 g/day is approximately equivalent to half cup/day of broccoli.

Table 3. Multivariable HRs[a] for postdiagnosis cruciferous vegetable intake in association with recurrence and total mortality stratified by ER status, stage, and tamoxifen therapy, ABCPP ($n = 11{,}390$)

	Recurrence				Total mortality			
	ER^+		ER^-		ER^+		ER^-	
Cruciferous vegetable intake	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
Study-specific quartiles (g/d)[b]								
Q1	252	1.00 (Ref.)	76	1.00 (Ref.)	332	1.00 (Ref.)	111	1.00 (Ref.)
Q2	254	0.99 (0.83–1.18)	93	1.28 (0.94–1.74)	311	0.98 (0.84–1.15)	106	1.00 (0.76–1.31)
Q3	248	0.95 (0.80–1.13)	89	1.15 (0.84–1.57)	305	0.96 (0.82–1.12)	99	0.89 (0.67–1.17)
Q4	281	1.05 (0.88–1.25)	90	1.26 (0.92–1.72)	299	0.93 (0.79–1.09)	112	1.11 (0.84–1.45)
P_{trend}		0.65		0.27		0.35		0.13
$P_{interaction}$		0.77				0.53		
	Stage I–II		**Stage III**		**Stage I–II**		**Stage III**	
Study-specific quartiles (g/d)								
Q1	234	1.00 (Ref.)	102	1.00 (Ref.)	331	1.00 (Ref.)	123	1.00 (Ref.)
Q2	259	1.11 (0.93–1.33)	98	1.02 (0.77–1.36)	316	1.05 (0.89–1.22)	111	0.95 (0.73–1.23)
Q3	252	1.02 (0.85–1.22)	95	0.99 (0.75–1.33)	289	0.92 (0.79–1.08)	130	1.10 (0.85–1.41)
Q4	274	1.14 (0.95–1.36)	107	1.05 (0.79–1.39)	304	1.02 (0.87–1.20)	121	0.94 (0.73–1.22)
P_{trend}		0.28		0.82		0.60		0.72
$P_{interaction}$		0.44				0.76		
	Tamoxifen		**No tamoxifen**		**Tamoxifen**		**No tamoxifen**	
Study-specific quartiles (g/d)[c]								
Q1	203	1.00 (Ref.)	47	1.00 (Ref.)	256	1.00 (Ref.)	69	1.00 (Ref.)
Q2	192	0.93 (0.76–1.13)	59	1.24 (0.84–1.83)	241	0.97 (0.81–1.15)	62	0.95 (0.67–1.35)
Q3	197	0.94 (0.77–1.15)	50	1.01 (0.68–1.52)	228	0.92 (0.77–1.11)	71	1.10 (0.78–1.53)
Q4	213	1.02 (0.84–1.24)	67	1.19 (0.80–1.75)	225	0.91 (0.76–1.10)	73	1.04 (0.74–1.47)
P_{trend}		0.76		0.78		0.30		0.87
$P_{interaction}$		0.53				0.28		

[a]HRs were from delayed-entry Cox proportional hazards regression models adjusted for age at diagnosis, ER/PR status (when applicable), TNM stage (when applicable), surgery, chemotherapy, radiotherapy, hormonal therapy (when applicable), smoking, BMI, exercise, menopausal status, race/ethnicity, and education. Study was included as a stratification variable.

[b]Analyses stratified by ER status exclude 320 women missing ER status.

[c]Among women with ER^+ cancer ($n = 8{,}257$), exclude women missing tamoxifen therapy information ($n = 38$).

Table 2 presents multivariable HRs for the association of cruciferous vegetable intake and breast cancer outcomes. Adjusting for age at diagnosis, stage, ER/PR status, cancer treatment, sociodemographics, smoking, BMI, exercise, and menopausal status, cruciferous vegetable intake was not associated with breast cancer recurrence or total mortality. Additional adjustment for red meat intake (g/day) did not alter results (data not shown).

We also investigated cruciferous vegetable intake with breast cancer-specific and non-breast cancer mortality. Compared with quartile 1, HRs (95% CIs) by increasing quartiles were 1.15 (0.97–1.37), 1.01 (0.85–1.20), and 1.09 (0.92–1.30) for breast cancer specific-mortality ($P_{trend} = 0.72$), and 0.83 (0.66–1.02), 0.94 (0.76–1.16), and 0.86 (0.69–1.08) for non-breast cancer mortality ($P_{trend} = 0.77$). Differences in dietary assessments precluded our ability to assess associations between specific types of cruciferous vegetables and breast cancer outcomes across all cohorts, with the exception of broccoli across the U.S. cohorts. Compared with quartile 1, HRs (95% CIs) by increasing tertiles of broccoli intake (g/day) were 1.00 (0.86–1.17) and 1.04 (0.89–1.20) for recurrence and 0.95 (0.83–1.10) and 0.94 (0.82–1.08) for mortality.

The association of cruciferous vegetables and breast cancer outcomes did not vary by ER status or stage (Table 3). We also examined the association of cruciferous vegetables and breast cancer outcomes by tamoxifen therapy (13), and none of the associations varied by tamoxifen use (Table 3).

Discussion

In this prospective pooled analysis of 11,390 breast cancer survivors from the United States and China, cruciferous vegetable intake assessed via FFQ at approximately 2 years after diagnosis was not associated with breast cancer recurrence or total mortality, overall or among subgroups defined by ER status, stage, and tamoxifen therapy. Our findings, from the largest study to date, do not support an association between intake of cruciferous vegetables after diagnosis and breast cancer outcomes.

In 2007, the WHEL Study reported that a major increase in vegetable (including cruciferous), fruit, and fiber intake, and a decrease in dietary fat intake were not associated with breast cancer outcomes (15). Cruciferous vegetable intake in the intervention group increased from 0.46 to 0.70 servings/day at year 1, and about half this increase was maintained through year 4 (14). In 2011, a secondary cohort analysis of the WHEL study reported a statistically significant inverse association for higher cruciferous vegetable intake at baseline and recurrence among tamoxifen users, but not among tamoxifen nonusers (13). In our analysis, which included WHEL participants from the control group only, cruciferous vegetable intake was not associated with breast cancer outcomes either among tamoxifen users or nonusers. We also conducted an analysis including the intervention group, and results were similar to presented findings (data not shown). Our overall findings are consistent with a report by Beasley and colleagues ($n = 4{,}441$), which reported no association of cruciferous vegetable intake with breast cancer survival; however, findings were not reported by tamoxifen therapy (16).

Strengths of the present study include the large sample size and the inclusion of well-designed prospective cohort studies from the United States and Shanghai, China with information on known clinical prognostic factors and postdiagnosis lifestyle factors. By conducting a pooled analysis with individual study data, we were able to use standardized statistical methods and definitions of covariates, thereby minimizing heterogeneity.

One limitation was that we were unable to examine individual types of cruciferous vegetables across cohorts due to differences in cruciferous vegetable questions on the FFQs by cohorts (see Table 1). The amount and type of bioactive compounds metabolized from cruciferous vegetables, such as ITCs, differ by the type of cruciferous vegetable (1), and some studies have reported no association for total cruciferous vegetables and risk of developing breast cancer, but observed associations for specific types (e.g., broccoli, turnips; refs. 10, 11). However, a recent pooled analysis of 20 studies reported no association of cruciferous vegetables (any type) or specific types with risk of developing breast cancer (12). Furthermore, we found no association between broccoli and outcomes among ABCPP U.S. participants. Finally, despite using different questionnaires, intake of total cruciferous vegetables across the U.S. cohorts was comparable, suggesting that similar dietary components were assessed.

Total energy intake, fruit intake, and noncruciferous vegetable intake were not available across all studies to consider as potential confounders, as the SBCSS used a 29-item abbreviated FFQ focused on habitual consumption of major food groups of interest (i.e., cruciferous vegetables, soy foods, meat, and fish). However, the U.S. studies had total energy intake available, and results among U.S. women were unaltered after adjustment for this factor (data not shown). We also lacked data on measured ITCs, one of the major biologic compounds in cruciferous vegetables thought to play a role in cancer-preventative mechanisms (1, 2, 5, 7, 8). One study reported an inverse association between risk of developing breast cancer and urinary ITC levels, but no association for cruciferous vegetable intake based on an FFQ and breast cancer (9). The amount of ITCs varies by type of cruciferous vegetable, geographical region, and cooking method (e.g., boiling, steaming, or raw consumption); therefore, intake based on FFQs may not be sensitive enough to adequately reflect internal exposure to ITCs (1, 9). Interindividual differences in metabolism of ITCs and consumption of other types of vegetables may also influence internal exposure (4). Future studies that directly measure urinary ITCs may be informative.

In conclusion, our results from a pooled prospective analysis of 11,390 U.S. and Chinese breast cancer survivors do not provide evidence for an association between postdiagnosis cruciferous vegetable consumption and breast cancer prognosis, overall or by ER status, stage, or tamoxifen therapy. However, direct measurement of urinary ITCs may be more informative, and future studies should consider measurement of both cruciferous vegetable intake and biomarkers of ITC exposure.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B.J. Caan, W.Y. Chen, W. Lu, X.-O. Shu
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