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Usual Cruciferous Vegetable Consumption and Ovarian Cancer: A Case-Control Study

Hallie McManus[1], **Kirsten B. Moysich**[2], **Li Tang**[2], **Janine Joseph**[2], and **Susan E. McCann**[2]

[1]Science Research Program, Horace Greeley High School, Chappaqua, NY

[2]Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY

Abstract

Ovarian cancer is the fifth leading cause of cancer-related deaths among women, primarily due to diagnosis at late stages. Therefore, identification of modifiable risk factors for this disease is warranted. Using the Patient Epidemiology Data System (PEDS), collected from 1981 to 1998 at Roswell Park Cancer Institute, Buffalo, NY, we conducted a hospital-based, case-control analysis of self-reported cruciferous vegetable intake and ovarian cancer among 675 women with primary, incident ovarian cancer and 1275 without cancer. Cruciferous vegetable intake was queried using a 44-item food frequency questionnaire (FFQ). Odds ratios (OR) and 95% confidence intervals (CI) were estimated with logistic regression, adjusting for age, body mass index (BMI), education, smoking status, parity, family history of ovarian cancer, total fruit consumption, total meat consumption, and total non-cruciferous vegetable consumption. We observed a significant inverse association for women with highest versus lowest intakes of total vegetables (OR=0.65, 95% CI=0.46–0.92), cooked cauliflower (OR=0.82, 95% CI=0.67–0.99), and cooked greens (OR=0.63, 95% CI=0.46–0.86) and an inverse, dose-dependent association between cooked cruciferous vegetables intake and ovarian cancer (for each additional ten servings per month, OR=0.85, 95% CI=0.76–0.96). These findings suggest that a diet that includes cruciferous vegetables could be an important modifiable risk factor for ovarian cancer.

Keywords

cruciferous; vegetables; ovarian cancer

Introduction

Ovarian cancer accounts for 5% of cancer-related deaths among women (1). In 2017, approximately 22,440 new cases and 14,080 deaths are expected to occur(2). Although the five-year survival rate of cases diagnosed at a local stage is 92%, the overall death rate for all ovarian cancer is 64%, as only 15% of cases are diagnosed at a local stage (1). There are currently no effective screening methods to detect early stage disease, and ovarian cancer

Corresponding author: Susan E. McCann, Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, susan.mccann@roswellpark.org, Fax: 716-845-8487.

Novelty and impact: The results of this study suggest that cruciferous vegetables may be a viable modifiable risk factor for reducing ovarian cancer risk, although the effect differs by cruciferous vegetable and preparation method.

symptoms are nonspecific—bloating, pelvic/abdominal pain, difficulty eating or feeling full quickly—making early detection difficult (1). Therefore, identification of modifiable risk factors for this disease is warranted.

The constituents of cruciferous vegetables (*Brassica*) have been previously shown to be inversely associated with risk of various cancer types including gastric, breast, lung, prostate, bladder, colorectal and endometrial cancers (1, 3–7). Cruciferous vegetables include, but are not limited to: broccoli, cauliflower, cabbage, collard greens, kale, and Brussels sprouts (8). Crucifers contain high levels of glucosinolates, which are phytochemicals that can be converted into isothiocyanates (ITC) during food preparation and digestion (9). ITCs are promising chemopreventive agents due to their multifaceted anti-cancer activities, including altering the metabolism of carcinogens, inhibiting tumorigenesis, inducing apoptosis and autophagy, arresting cell proliferation, inhibiting angiogenesis and metastasis, suppressing inflammatory mediators, activating immune defenses, impacting cancer cell energetics and metabolism, and generating reactive oxygen species (10). Given these anti-carcinogenic activities, cruciferous vegetables may represent a viable modifiable risk factor important in ovarian cancer etiology. Therefore, utilizing a case-control study design, we examined the association between self-reported usual intakes of several cruciferous vegetables and ovarian cancer in archived data from Roswell Park Cancer Institute (RPCI).

Materials and Methods

The Patient Epidemiologic Data Systems study (PEDS) was conducted from 1981 to 1998, wherein all patients seen at RPCI to be evaluated for potential cancer diagnoses were given a self-administered epidemiologic questionnaire that encompassed health, reproductive, lifestyle (cigarette smoking, physical activity, diet), occupational, and other epidemiologic factors. The protocol for the study was approved by the RPCI Institutional Review Board, and completion and return of the questionnaire implied consent. Approximately 50% of those offered participation returned completed questionnaires. The final dataset includes patients who received a definitive cancer diagnosis (cases) and those with benign conditions (controls). For this analysis, we selected all women who had received a diagnosis of invasive cancer of the ovary, peritoneum, or fallopian tubes and women without a cancer diagnosis with at least one intact ovary, matched to the cases on five-year age strata. Women who answered 23 or fewer food frequency questions and women with a history of a stomach ulcer or who had previously had a hysterectomy were excluded from the analysis, resulting in 675 cases and 1275 controls for analyses.

Information regarding diet and cruciferous vegetable consumption in the few years prior to diagnosis was obtained using a 44-question food frequency questionnaire (FFQ) which was developed through a regression approach from data obtained from extensive diet records (11). Although not directly validated, the brief FFQ includes cruciferous vegetables commonly consumed. The cruciferous vegetable category included the majority of those commonly consumed among western populations: broccoli, cauliflower, cabbage, Brussels sprouts, and greens (such as kale, mustard green, and collard greens). Additionally, several crucifers were queried as both raw and cooked, since bioavailability of ITCs is dependent upon this factor. Frequency categories ranging from never to 5–7 times per week were converted to total monthly consumption, and intakes were expressed as individual items, raw and cooked combined, and total cruciferous vegetables. To account for diet composition, food group variables were created to represent total fruits, total vegetables, and total meats consumed and were included as covariates in the statistical analyses.

Statistical Analysis.

All analyses were performed with SAS for Windows, version 9.4 (Cary, NC) and were considered statistically significant at $p<0.05$. Descriptive statistics were calculated including Student's t-test for continuous variables and Pearson's chi-square for categorical variables. To calculate associations between ovarian cancer and food group consumption (fruits, meats, vegetables, non-cruciferous vegetables, cruciferous vegetables, raw cruciferous vegetables, and cooked cruciferous vegetables), monthly consumption was divided into quintiles based on the distributions in the controls. As consumption of individual crucifers was low, in general, to examine the association between ovarian cancer and specific cruciferous vegetables, we divided the study sample into two groups, with 0.5 servings per month as the cut point (≤ 0.5 vs >0.5 servings per month). Associations with ovarian cancer in each category were estimated with odds ratios (ORs) and 95% confidence intervals (CIs) calculated using unconditional logistic regression with respect to the lowest (referent) quantile. Odds ratios were adjusted for possible confounders, including age, body mass index (BMI, education, smoking status, family history of ovarian cancer, parity, total fruit consumption, total meat consumption, and total consumption of non-cruciferous vegetables. Covariates were retained if they had a p-value of <0.20 in logistic regression models or if inclusion altered the observed ORs by >15%.

Results

Shown in Table 1 are the descriptive characteristics of ovarian cancer cases and controls. Cases were less likely ever to have smoked, used oral contraceptives, or had a tubal ligation. Age, BMI, education, family history of ovarian cancer, and parity did not differ significantly between cases and controls.

Odds ratios and 95% confidence intervals for associations between ovarian cancer and food group intakes are shown in Table 2 and associations between ovarian cancer and intakes of individual crucifers are shown in Table 3. We observed significantly lower odds of ovarian cancer for women with the highest intake of total vegetables (OR=0.65, 95% CI=0.46–0.92), cooked cauliflower (OR=0.82, 95% CI=0.67–0.99), and cooked greens (OR=0.63, 95% CI=0.46–0.86). There was a non-significant inverse dose-dependent association between quintiles of cooked cruciferous vegetables intake and ovarian cancer. This association achieved statistical significance when cooked cruciferous vegetables intake was parameterized as a continuous variable (for each additional ten servings per month, OR=0.85, 95% CI=0.76–0.96, data not shown). No associations were observed for non-cruciferous vegetables (OR=0.86, 95% CI=0.59–1.26), total cruciferous vegetables (OR=0.72, 95% CI=0.51–1.02), total broccoli (OR=0.80, 95% CI=0.64–1.02), raw broccoli (OR=0.91, 95% CI=0.74–1.13), cooked broccoli (OR=0.87, 95% CI=0.70–1.10), and total cauliflower (OR=0.83, 95% CI=0.68–1.02). We also observed a statistically significant positive association between total meat consumption and ovarian cancer (OR=1.86, 95% CI=1.36–2.55).

Discussion

Our findings suggest that cooked cruciferous vegetables, largely driven by cooked cauliflower and greens, and total vegetables, may be viable modifiable risk factors for ovarian cancer. Currently, the nonspecific nature of ovarian cancer symptoms makes it difficult to detect this disease at early stages (1). Current methods for high-risk women (women with familial history of ovarian cancer) include the cancer antigen 125 (CA-125) blood test and transvaginal ultrasounds (TVUS); both tests are, however, flawed(12). The CA-125 blood test, which looks for abnormally high blood levels of a surface protein typically found on ovarian cancer cells, does not account for other, non-cancerous factors that can lead to high CA-125 levels, nor is it elevated in all women with ovarian cancer (12). TVUS identifies abnormal masses; however, the test cannot differentiate between cancerous and benign masses, requiring further invasive tests, such as biopsies (12). Unlike high-risk women, average-risk women typically only receive pelvic exams, which rarely, if ever, detect ovarian cancer in the early stages, as growths are usually undetectable until the later, more aggressive stages (12). As demonstrated in the UK Collaborative Trial of Ovarian Cancer Screening, in which over 200,000 average-risk women were randomized to different ovarian cancer screening arms and followed for nearly 15 years, there is no definitive evidence that population-level multimodal screening (repeated CA-125 measures and TVUS) for ovarian cancer reduces disease-specific mortality (13). Therefore, identification of modifiable risk factors for this disease is warranted, as it provides a means for women (high-risk or not) to lower their risk for disease.

There has been a growing interest in the role cruciferous vegetables play in cancer. Meta-analyses, which have examined the overall implications of cruciferous vegetables in the diet, have shown an inverse association between these foods and ovarian cancer (14–16). In this study, we observed a non-significant inverse association between total cruciferous vegetable intakes and ovarian cancer risk. We conducted a regression analysis to identify which subgroups contributed most notably to the total cruciferous category. Our results showed that cooked broccoli, raw cauliflower, raw cabbage, cooked cauliflower, and cooked greens, respectively, were the greatest contributors to the total cruciferous vegetable group. Alone, cooked cauliflower and cooked greens were statistically significantly inversely associated with ovarian cancer, but null associations were observed in the cooked broccoli, raw cauliflower, and raw cabbage categories, driving the overall non-significant association between cruciferous vegetables and ovarian cancer.

The nutrient density and nutritional benefits of raw versus cooked foods has been of growing interest (17, 18). Previous studies suggest that the cooking process may denature enzymes and nutrients; however, in some cases, cooking can increase the bioavailability of certain nutrients (19). Cruciferous vegetables contain glucosinolates in their cytoplasm. Disruption of the cell wall through chewing or cutting brings these compounds into contact with the enzyme myrosinase, with subsequent formation of isothiocyanates (19). However, the cooking process reduces the conversion of glucosinolates into the bioactive compounds isothiocyanates (20). Contrary to previous studies, our results did not support a strong effect for the raw cruciferous category, although there was a significantly reduced odds of ovarian cancer associated with consumption of cooked crucifers. These differences might have occurred because many of the subgroups of cruciferous vegetables are rarely eaten raw, especially during the time period which the data was collected. The small variability in the subjects' monthly consumption of raw cruciferous vegetables might have made an association with ovarian cancer difficult to detect. There was greater variability in consumption of cooked cruciferous vegetables. There was a suggestion of a threshold effect in the total cruciferous and cooked cruciferous vegetables categories at the highest levels of intake (>15 servings/month). It is possible that a similar threshold in the raw cruciferous vegetable association, if one existed, was not apparent, due to the lower overall consumption of raw cruciferous vegetables in our population. Among individual cruciferous vegetables, the significant inverse association was only observed with cooked cauliflower and cooked greens, raising a possibility that other by-products of glucosinolates, instead of ITCs, may be key players in associations with ovary cancer, since the yield of ITCs is generally attenuated by cooking process; however, other by-products of glucosinolates may be increased under such conditions (21, 22). If the potential beneficial role of cruciferous vegetables in prevention of ovarian cancer could be validated, further investigation on cooking and products of glucosinolates is warranted.

Of the patients who received this survey, only about half responded, suggesting voluntary response bias may have played a role, as those who did respond may have been less likely to have a serious condition. Further, non-response bias may have played a role in the results of our study, as those patients with more severe cases of OC may have been less likely to respond. Response bias is a problem in any survey. However, both cases and controls were patients at RPCI and therefore it is unlikely that recall would be differential as both groups were being seen for diagnosis.

There were some limitations to the FFQ used, as it only included 44 items. Although this did not a pose a problem in the unadjusted analysis, as the FFQ had a strong focus on cruciferous vegetables, it potentially limited the usefulness of certain of the covariates. For instance, processed and red meats were the focus of the PEDS FFQ, so the analysis is limited in its ability to consider other sources of meat, such as poultry, that are more commonly consumed in the population. On the other hand, given the correlated nature of food use, the foods that were included on the FFQ likely captured sufficient variation in diet quality in these data. Additionally, the 44-item FFQ was not directly validated for estimation of cruciferous vegetable intake. Similar FFQs have validity coefficients in the range of 0.49–0.69 for broccoli; therefore we expect that our FFQ performs comparably (23, 24).

Our study suggests that consumption of cruciferous vegetables, specifically cooked cauliflower and cooked greens, may be viable modifiable risk factors for ovarian cancer. Our findings also revealed that there may be a threshold effect present in the association between cruciferous vegetable consumption and ovarian cancer risk, meaning in order to have the observed inverse association a certain quantity of crucifers must be consumed. These results propose that a diet that includes cruciferous vegetable consumption, along with other healthy lifestyle habits, may contribute to decreasing risk for ovarian cancer.

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Abbreviations:

BMI	Body mass index
PEDS	Patient Epidemiologic Data System
FFQ	food frequency questionnaire
OR	odds ratio
CI	confidence interval
ITC	isothiocyanates
RPCI	Roswell Park Cancer Institute
TVUS	transvaginal ultrasound

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Table 1.

Descriptive Characteristics of Ovarian Cancer Cases and Hospital Controls: Roswell Park Cancer Institute, Buffalo, NY (1981-1998)

	Cases (n = 675)	Controls (n = 1275)	p-value
	Mean ± SD		
Age	55.2 ± 14.0 *	55.1 ± 14.3 *	0.8157
BMI	25.5 ± 5.5 *	25.5 ± 5.3 *	0.8960
	Number (%)		
Education ≤ High School At least some college	369 (54.7) † 306 (45.3)	683(53.6) 592 (46.4)	0.6435
Smoking Status Current Former Never	84 (12.4) † 219 (32.4) 372 (55.1)	237 (18.6) 412 (32.3) 626 (49.1)	0.0013
Family History of Ovarian Cancer Yes No	28 (4.2) † 647 (95.9)	48 (3.8) 1227 (96.2)	0.6772
Parity 0 ≥ 1	156 (23.1) † 519 (76.9)	267(20.9) 1008 (79.1)	0.2687
Oral Contraceptive Use Ever Never	199 (29.5) † 476 (70.5)	436 (34.2) 839(65.8)	0.0346
History of Tubal Ligation Yes No	78 (11.6) † 597 (88.4)	209 (16.4) 1066 (83.6)	0.0041
Total Fruit Consumption (SPM) Q1 (11.3[1]) Q2 (29.0) Q3 (44.5) Q4 (62.0) Q5 (90.5)	127 (18.8) † 141 (20.9) 133 (19.7) 155 (23.0) 119 (17.6)	269 (21.1) 251 (19.7) 245 (19.2) 259 (20.3) 251 (19.7)	0.4131
Total Meat Consumption (SPM) Q1 (6.5) Q2 (14.5) Q3 (22.0) Q4 (32.0) Q5 (52.0)	102 (15.1) † 145 (21.5) 128 (19.0) 131 (19.4) 169 (25.0)	255 (20.0) 270 (21.2) 250 (19.6) 245 (19.2) 255 (20.0)	0.0262
Total Consumption of Cruciferous Vegetables (SPM) Q1 (4.0) Q2 (7.0) Q3 (11.5) Q4 (22.0) Q5 (40.0)	159 (23.6) † 117 (17.3) 146 (21.6) 148 (21.9) 105 (15.6)	278 (21.8) † 232 (18.2) 259 (20.3) 254 (19.9) 252 (19.8)	0.1787
Total Consumption of Non-Cruciferous Vegetables (SPM) Q1 (26.0) Q2 (45.0) Q3 (60.0) Q4 (77.5) Q5 (107.0)	125 (18.5) † 151 (22.4) 147 (21.8) 142 (21.0) 110 (16.3)	256 (20.1) 258 (20.2) 257 (20.2) 253 (19.8) 251 (19.7)	0.2753

[1]Quintile median servings per month (SPM); Q=quintile.

†Tested by chi-squared to test for differences in proportion

*Tested by t-test for differences in means

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Table 2.

Association between Ovarian Cancer and Intake of Cruciferous Vegetables and Other Food Groups of Interest

	n Cases	Controls	OR[1] (95% CI)
Total Meat (SPM)	102	255	1.00
Q1 (≤10.0)	145	270	1.35 (0.99-1.84)
Q2 (10.5-18.0)	128	250	1.32 (0.96-1.81)
Q3 (18.5-26.0)	131	245	1.40 (1.02-1.93)
Q4 (26.5-40.0)	169	255	1.85 (1.35-2.54)
Q5 (> 40.0)			
Total Fruit (SPM)	127	269	1.00
Q1 (≤19.5)	141	251	1.17 (0.86-1.58)
Q2 (20.0-36.5)	133	245	1.12 (0.82-1.54)
Q3 (37.0-52.0)	155	259	1.31 (0.95-1.79)
Q4 (52.5-74.5)	119	251	1.06 (0.75-1.49)
Q5 (> 74.5)			
Total Vegetables (SPM)	136	258	1.00
Q1 (≤44.5)	129	252	0.94 (0.69-1.27)
Q2 (45.0-63.5)	171	256	1.13 (0.84-1.53)
Q3 (64.0-85.5)	138	255	0.89 (0.64-1.22)
Q4 (86.0-115.5)	101	254	0.65 (0.46-0.92)
Q5 (> 115.5)			
Non-Cruciferous Vegetables (SPM)	125	256	1.00
Q1 (≤35.5)	151	258	1.13 (0.83-1.54)
Q2 (36.0-52.5)	147	257	1.08 (0.79-1.49)
Q3 (53.0-68.0)	142	253	1.04 (0.74-1.46)
Q4 (68.5-90.0)	110	251	0.86 (0.59-1.25)
Q5 (> 90.0)			
Total Cruciferous Vegetables (SPM)	159	278	1.00
Q1(≤5.5)	117	232	0.86 (0.64-1.17)
Q2 (6.0-9.0)	146	259	0.95 (0.71-1.28)
Q3 (9.5-16.0)	148	254	1.00 (0.73-1.36)
Q4 (16.5-28.5)	105	252	0.74 (0.52-1.05)
Q5 (> 28.5)			
Raw Cruciferous Vegetables (SPM)	203	388	1.00
Q1 (≤1.5)	92	144	1.13 (0.82-1.56)
Q2 (2.0-2.5)	170	340	0.97 (0.74-1.27)
Q3 (3.0-4.5)	95	165	1.13 (0.81-1.57)
Q4 (5.0-11.0)	115	238	1.09 (0.78-1.51)
Q5 (> 11.0)			
Cooked Cruciferous Vegetables (SPM)	175	308	1.00
Q1 (≤3.0)	153	268	1.00 (0.75-1.33)
Q2 (3.5-5.0)	108	192	0.97 (0.71-1.34)
Q3 (5.5-10.0)	134	261	0.89 (0.65-1.21)
Q4 (10.5-20.0)	105	246	0.74 (0.52-1.04)
Q5 (> 20.0)			

SPM = Servings per month; Q = quintile; OR=odds ratio; CI=confidence interval

[1] Adjusted for Age, BMI, Smoking history, Education, Parity, Family History of Ovarian Cancer, and other (non-overlapping) food groups.

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Table 3.

Association between Ovarian Cancer and Intake of Specific Cruciferous Vegetables

	n (%)		OR[1] (95% CI)
	Cases	Controls	
Total Broccoli			
≤ 0.5 SPM	185	292	1.00
> 0.5 SPM	490	983	0.80 (0.64-1.02)
Raw Broccoli			
≤ 0.5 SPM	420	747	1.00
> 0.5 SPM	255	528	0.91 (0.74-1.13)
Cooked Broccoli			
≤ 0.5 SPM	202	341	1.00
> 0.5 SPM	473	934	0.87 (0.70-1.10)
Total Cabbage			
≤ 0.5 SPM	285	554	1.00
> 0.5 SPM	390	721	1.04 (0.85-1.28)
Raw Cabbage			
≤ 0.5 SPM	326	644	1.00
> 0.5 SPM	349	631	1.10 (0.90-1.35)
Cooked Cabbage			
≤ 0.5 SPM	451	848	1.00
> 0.5 SPM	224	427	0.99 (0.80-1.22)
Total Cauliflower			
≤ 0.5 SPM	272	462	1.00
> 0.5 SPM	403	813	0.83 (0.68-1.02)
Raw Cauliflower			
≤ 0.5 SPM	441	814	1.00
> 0.5 SPM	234	461	0.97 (0.78-1.19)
Cooked Cauliflower			
≤ 0.5 SPM	312	532	1.00
> 0.5 SPM	363	743	0.82 (0.67-0.99)
Brussels Sprouts			
≤ 0.5 SPM	501	946	1.00
> 0.5 SPM	174	329	1.07 (0.86-1.34)
Cooked Greens[2]			
≤ 0.5 SPM	614	1099	1.00
> 0.5 SPM	61	176	0.63 (0.46-0.86)

SPM = Servings per month; OR=odds ratio; CI=confidence interval

[1]Adjusted for Age, BMI, Smoking History, Education, Parity, Family History of Ovarian Cancer, Total Fruit Consumption, Total Meat Consumption and Non-Cruciferous Vegetable Consumption.

[2]Includes dandelion, turnip, collard, mustard greens, kale