Original Article

Intake of cruciferous vegetables is associated with reduced risk of ovarian cancer: a meta-analysis

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Background: Epidemiological studies on the association between cruciferous vegetable (CV) consumption and the risk of ovarian cancer have demonstrated inconsistent results. We conducted a meta-analysis on CV consumption and ovarian cancer risk. **Methods**: The relevant studies were identified by searching the Medline (Pubmed), Embase and Web of Science databases. The references of related articles and reviews up to October 2013 were also screened. The pooled relative risks (RRs) with 95% confidence intervals (CIs) for the highest versus the lowest CV consumption levels were calculated using a random-effects model. The heterogeneity and publication bias were also evaluated. **Results**: Eight studies (4 case-control studies and 4 cohort studies) were identified and included in this meta-analysis. When all studies were pooled together, there was a significantly inverse association between CV consumption and the risk of ovarian cancer (RR: 0.89; 95% CI: 0.81-0.99). No significant heterogeneity or publication bias was found. **Conclusions**: The findings from this study suggest that the consumption of CVs may reduce the risk of ovarian cancer. Further investigations are needed to confirm the clinical effect of CVs on ovarian cancer.

Key Words: cruciferous vegetables, ovarian cancer, epidemiological study, cancer prevention, meta-analysis

INTRODUCTION

Ovarian cancer is the sixth most commonly diagnosed cancer among women and is the second most common cause of gynaecologic cancer mortality worldwide.[1,2] The majority of ovarian cancer patients are diagnosed at an advanced stage with a dismal prognosis.[3,4] Previous studies have demonstrated that factors, such as parity, oophorectomy, oral intake of contraceptives and breastfeeding, are inversely related with the risk of ovarian cancer.[2,5-7] However, effective measures for the active prevention of this malignant disease have yet to be discovered.

Cruciferous vegetables (CV) belong to the family Brassicaceae, which include broccoli, cabbage, cauliflower, bok choy, and other similar green, leafy vegetables. Glucosinolate is one of the components in CV, and it is the precursor of isothiocyanate and indole-3-carbinol (I3C), and both of these products are associated with a reduced risk of a variety of cancers.[8-10] A recently published meta-analysis demonstrated an inverse relationship between cruciferous vegetable consumption and the risk of a number of cancers, such as breast cancer, bladder cancer, prostate cancer, and colorectal cancer;[11-15] however, the findings on the relationship between CV intake and ovarian cancer are inconsistent.[16-23] The purpose of this meta-analysis was to evaluate the association between CV consumption and the risk of ovarian cancer.

Methods

Literature search

A systematic search of the relevant studies was conducted from the Medline (Pubmed), Embase and Web of Science databases up to October 12, 2013. The following search terms were used: ('cruciferous vegetables' OR cruciferae OR brassicaceae OR 'brassica vegetables' OR broccoli OR cabbage OR cauliflower OR 'brussel sprouts' OR 'mustard plants' OR 'cole slaw' OR collards OR 'bok choy' OR 'turnip greens') AND ovarian AND (tumour OR neoplasm OR cancer OR carcinoma). The reference lists of the related articles and reviews were investigated for additional information.

Selection criteria

The eligible studies met the following criteria: (1) published in English; (2) case-control or cohort design; (3) evaluated the association between CV consumption and ovarian cancer; and (4) relative risks (RR) and odds ratio (OR) estimates with 95% confidence intervals (CI) reported (or the data necessary to calculate these factors). In cases of multiple studies using the same population, only the most recent or most informative study was included.

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Data extraction and quality assessment

The data extraction was conducted by two independent investigators. The data included the first author's name, publication year, study region, study period, study design, age, sample size (cases or controls and cohort size), measures and types of CVs and consumption categories, multivariate adjusted ORs or RRs with their 95% CIs for the highest category of CV consumption compared with the lowest category, and the matching and adjusted covariates.

The quality of each study was assessed by two independent investigators on the basis of the nine-score Newcastle-Ottawa Scale (NOS).[15,24]

Statistical analysis

The adjusted RRs were used for the meta-analysis. Due to the low incidence of ovarian cancer, the OR in the case-control study was similar to the RR.[25] A random-effects model was applied to pool the risk estimates. The possible heterogeneity was assessed using a Q-test and I^2. $p<0.1$ was considered significant for heterogeneity with the Q-test; <25%, 25-75%, >75% represented the low, median and high levels of heterogeneity for the I^2 variable. For studies that reported separate results for different types of CVs, we used a fixed-effects model to obtain the overall RR.[15] A subgroup analysis was performed according to the study design, type of CV, quality of the studies and specific adjustments. The publication bias was evaluated using Egger's test, and $p<0.1$ was considered significant. The STATA12.0 software (StataCorp, College Station, TX, USA) was used for statistical analysis. A two-sided $p<0.05$ was considered significant.

RESULTS

Literature search

A total of 8 studies[16-23] were included in this meta-analysis on the association between CV intake and ovarian cancer. The process of identifying and selecting articles is shown in Figure 1.

Study characteristics and quality assessment

The main characteristics of the 8 included articles are shown in Table 1. Among these studies, four are cohort studies; two are population-based, case-controlled studies;[19,22] and two are hospital-based, case-controlled studies.[16,23] The sample sizes of the cohort studies ranged from 61084 to 97275. For case-controlled studies, the number of patients ranged from 254 to 1031, and the number of controls ranged from 652 to 11492. Three of the 8 studies were conducted in North America; 3 in Europe; 1 in Asia; and 1 in Australia. The quality score of each study (ranging from 6 to 9) is shown in Table 1. High quality studies (with a score no less than 7) included 4 cohort studies and 1 case-controlled study.

Risk estimation

In a random-effects meta-analysis of all 8 studies, a significant inverse association between high CV consumption and the risk of ovarian cancer was observed (RR: 0.89; 95% CI: 0.81-0.99) (Figure 2). There was low heterogeneity among the studies ($p=0.36$, $I^2=9.7\%$), and no publication bias was found with Egger's test ($p=0.50$). A

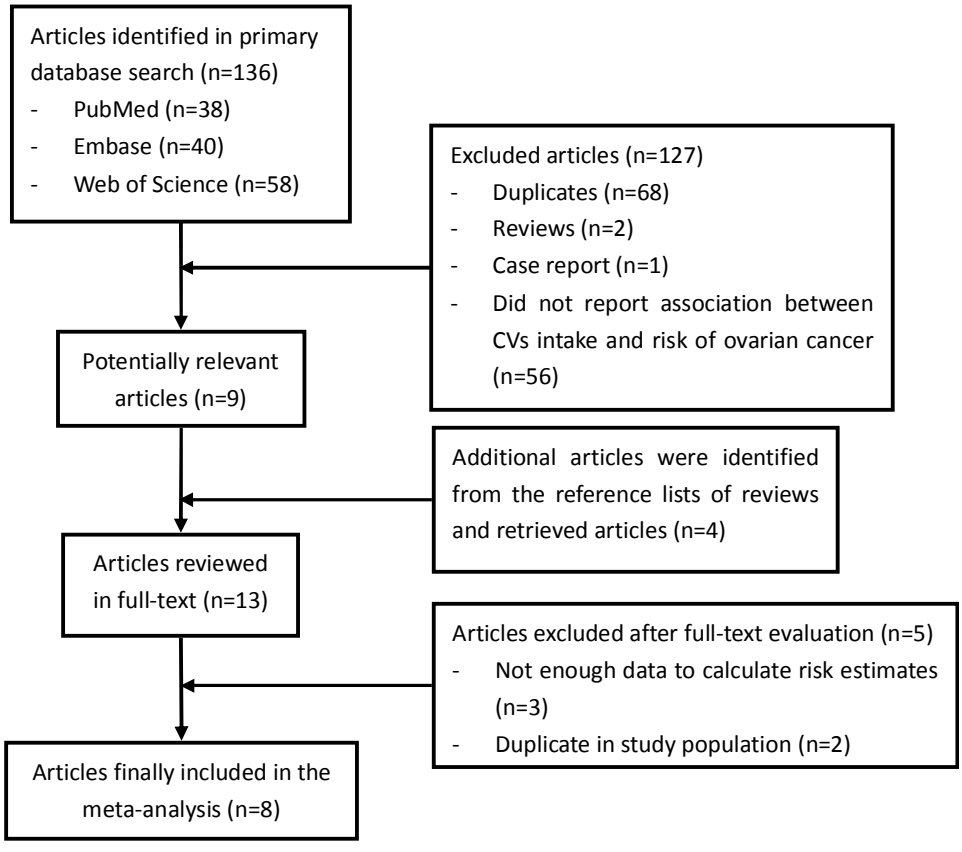

Figure 1. Process of study selection for meta-analysis

Table 1. Main characteristics of the included studies evaluating the association between CV intake and the risk of ovarian cancer

Author (year)	Country	Study design†	Age (y)	Study period	Number of participants (cases)	Study quality	Diet assessment	Type of CVs and consumption categories	Risk estimates (95% CI)	Adjustment for confounders
Bosetti[16] (2012)	Italy	HBCC	NA‡	1991-2009	12523 (1031)	6	Validated FFQ§	Cruciferous vegetables One portion/week of CVs	 0.87 (0.74, 1.03)	Age, study centre, year of interview, education, alcohol drinking, smoking, BMI, total energy intake, parity, menopause status, age at menopause, oral contraceptive use, hormone use.
Kolahdooz[19] (2009)	Australia	PBCC	18-79	1990-1993	1460 (683)	6	Validated FFQ	Cruciferous vegetables Group 1 (ref.) Group 2 Group 3 Group 4	 1.00 1.00 (0.73, 1.37) 1.11 (0.80, 1.55) 1.16 (0.81, 1.67)	Age, age squared, oral contraceptive use, parity, education after high school, energy intake
Gates[18] (2007)	United States	Cohort	30-55	1976-2002	66940 (347)	8	Validated FFQ	Broccoli (servings) Never or <2/month (ref.) 2/month to <1/week 1/week 2+/week	 1.00 0.87 (0.59, 1.29) 0.80 (0.54, 1.17) 0.67 (0.45, 1.01)	Age, smoking, age at menarche, BMI, menopausal status, age at menopause, parity, oral contraceptive use, hormone use, hysterectomy, oophorectomy, tubal ligation, physical activity, family history of ovarian cancer.
Chang[17] (2007)	United States	Cohort	<85	1995-2003	97275 (280)	7	Validated FFQ	Cauliflower/brussels sprouts (g) 0.0 (ref.) >0.0-2.1 >2.1-4.1 >4.1-8.0 >8.0 Broccoli (g) ≤3.3 >3.3-7.8 >7.8-14.4 <14.4-23.5 >23.5 Mustard greens/turnip greens/ collards None Any Cabbage/coleslaw (g) 0.0 >0.0-1.1 >1.1-1.8 >1.8-3.6 >3.6	 1.00 0.87 (0.61, 1.25) 0.77 (0.54, 1.11) 0.86 (0.61, 1.22) 0.80 (0.56, 1.15) 1.00 1.03 (0.71, 1.50) 0.97 (0.66, 1.42) 1.24 (0.86, 1.79) 0.91 (0.61, 1.36) 1.00 1.01 (0.71, 1.44) 1.00 0.78 (0.53, 1.16) 0.89 (0.62, 1.29) 1.05 (0.74, 1.48) 1.12 (0.79, 1.59)	Age, race, total daily caloric intake, parity, oral contraceptives use, average strenuous physical exercise, alcohol drinking, menopause status, hormone use.

Table 1. Main characteristics of the included studies evaluating the association between CV intake and the risk of ovarian cancer (coun.)

Author (year)	Country	Study design[†]	Age (y)	Study period	Number of participants (cases)	Study quality	Diet assessment	Type of CVs and consumption categories	Risk estimates (95% CI)	Adjustment for confounders
Mommers[21] (2005)	Nether-land	Cohort	55-69	1986-1997	62573 (252)	9	Validated FFQ	Brussels sprouts Per 25-g day increment Cauliflower Per 25-g day increment Cabbage Per 25-g day increment Kale Per 25-g day increment	 0.78 (0.42, 1.44) 1.06 (0.68, 1.65) 1.19 (0.73, 1.96) 1.02 (0.31, 3.35)	Age, BMI, smoking, oral contraceptive use, parity, age at menarche and meno-pause, family history of ovarian or breast cancer, hysterectomy, tubal ligation, soci-oeconomic status.
Larsson[20] (2004)	Sweden	Cohort	38-76	1987-2003	61084 (266)	9	Validated FFQ	Cabbage (servings/week) 0 (ref.) 0.1 to <0.5 0.5 to <1.5 ≥1.5	 1.00 0.91 (0.67, 1.25) 0.88 (0.59, 1.32) 0.87 (0.58, 1.31)	Age, BMI, educational level, parity, oral contraceptive use, fish consumption, die-tary lactose intake
Pan[22] (2004)	Canada	PBCC	20-76	1994-1997	2577 (442)	8	Validated FFQ	Cruciferous vegetables Quartile 1 (ref.) Quartile 2 Quartile 3 Quartile 4	 1.00 0.81 (0.60, 1.10) 0.80 (0.59, 1.10) 0.76 (0.56, 0.99)	Age, education, living area, BMI, alcohol drinking, family income, marital status, ethnic group, total calorie intake.
Zhang[23] (2002)	China	HBCC	<75	1999-2000	906 (254)	6	Validated FFQ	Cruciferous vegetables (kg/year) ≤34.2 (ref.) 34.2-49.3 49.3-72.8 ≥72.8	 1.00 1.25 (0.8, 2.0) 0.82 (0.5, 1.4) 0.67 (0.4, 1.3)	Edible portions of foods, cooking methods used, seasonal factors, market availability, age, education, living area, BMI, smok-ing, alcohol drinking, tea drinking, family income, marital and menopause status, parity, tubal ligation, oral contraceptive use, physical activity, family history of ovarian cancer, total energy intake.

[†]HBCC: hospital-based, case-controlled study; PBCC: population-based, case-controlled study.
[‡]Only median ages were reported; the median age of cases and controls were both 58.
[§]Food frequency questionnaire.

sensitivity analysis was performed by sequentially removing one study at a time. The RR ranged from 0.87 (0.77-0.99) after omitting the study conducted by Chang et al[17] to 0.91 (0.82-1.01) after omitting the study conducted by Pan et al.[22] The results of the sensitivity analysis demonstrated that none of the 8 studies significantly affected the pooled risk estimates for the association between CV consumption and the risk of ovarian cancer.

Subgroup analysis

A series of subgroup analyses of CV intake and the risk of ovarian cancer were conducted according to type of CV, study design, quality score and adjustments. The summary of all subgroup analyses is shown in Table 2. The forest plots of all subgroup analyses are shown in Figure 3.

Different CV types

For the subgroup analysis according to different CV types, we focused on the relationship between two major types of CV (broccoli and cabbage) and the risk of ovarian cancer. An inverse association was observed for broccoli consumption (RR: 0.78, 95% CI: 0.58-1.06); however, there was no significant association for cabbage consumption (RR: 1.04, 95% CI: 0.83-1.32).

Study design

For the subgroup analysis according to the study design, a 13% reduction (RR: 0.87, 95% CI: 0.73-1.03) of ovarian cancer risk was demonstrated in case-controlled studies, and a 7% reduction (RR: 0.92, 95% CI: 0.80-1.07) was demonstrated in cohort studies. However, these findings were not significant.

Quality score

Among the 8 studies, five studies were regarded as high quality (a score no less than 7).[17,18,20-22] Similar results were demonstrated with the meta-analysis with high quality studies (RR: 0.89, 95% CI: 0.77-1.02) and the other 3 studies (RR: 0.91, 95% CI: 0.73-1.14).

Adjustments

For the subgroup analysis of studies with oral contraceptive use adjusted, 7 studies were included.[16-21,23] Although not statistically significant, there was a 10% reduction of ovarian cancer risk (RR: 0.91, 95% CI: 0.82-1.01). Three studies were included in the meta-analysis for hormone-use status,[16-18] and a 12% reduced risk of ovarian cancer was found with borderline significance (RR: 0.88, 95% CI: 0.77-1.01).

DISCUSSION

The exact cause of ovarian cancer is unknown, and only a few risk factors, such as genetic factors,[26-31] oral contraceptive use[32] and hormone use,[33] have been identified. Identifying other potential risk factors may facilitate our understanding of the etiology of ovarian cancer, thereby leading to the discovery of effective prevention methods. Previous systemic reviews and meta-analyses have reported that CV consumption is associated with a reduced risk of a variety of cancers.[11-15,24,34] However, the preventative effects on ovarian cancer have not been confirmed, and the published literature has revealed inconsistent results. Therefore, we performed a meta-analysis on this topic using all of the published data.

Our results demonstrated a significant relationship between CV consumption and a reduced risk of ovarian cancer. A 10% reduced risk was revealed by comparing the highest and lowest categories of CV consumption. This result is concordant with previously conducted meta-analyses investigating the association between CV consumption and the risk of other cancer types.[11-15,24,34]

In our subgroup analyses, a 22% reduction of ovarian cancer risk with marginal significance was found for broccoli but not for cabbage; however, most of the 8 studies did not report specific RRs (or ORs) for broccoli or cabbage consumption. Due to the limited number of studies, a firm conclusion cannot be drawn. The subgroup

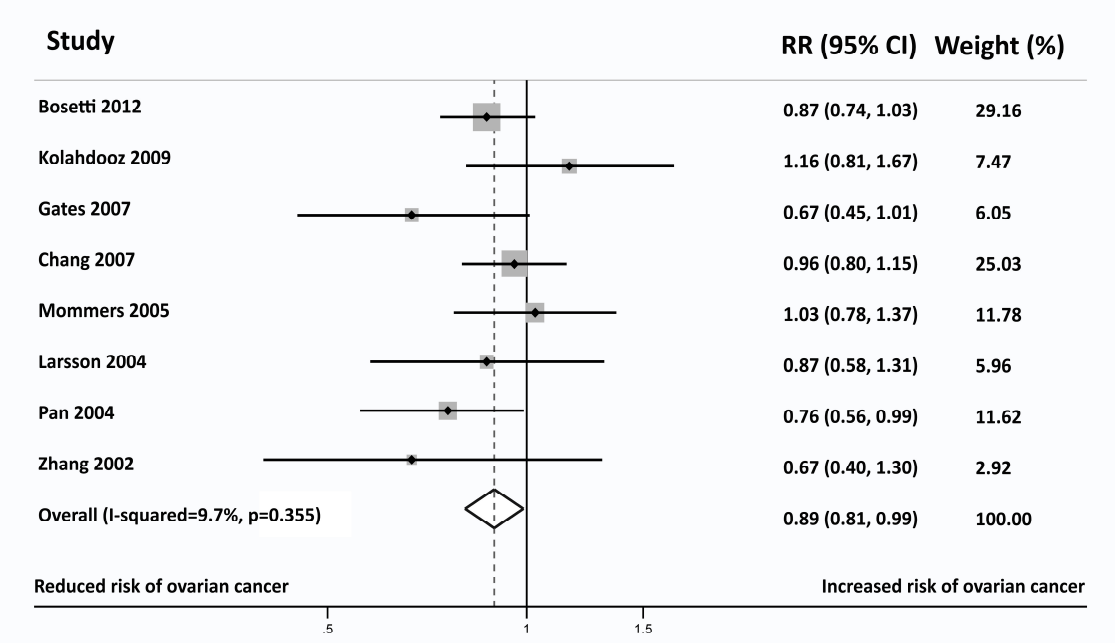

Figure 2. Forest plot (random-effects model) of CV consumption and the risk of ovarian cancer

Table 2. Summary of the pooled risk estimates of the association between CV intake and the risk of ovarian cancer according to subgroups

Subgroup analysis	Number of studies	Pooled RR (95% CI)	*p* value of Q-test	I^2 value (%)	*p* value of Egger's test
Types of CVs					
Broccoli	2	0.78 (0.58, 1.06)	0.29	10.0	N/A
Cabbage	3	1.04 (0.83, 1.32)	0.55	0.0	0.94
Study design					
Case-control study	4	0.87 (0.73, 1.03)	0.26	25.8	0.92
Cohort study	4	0.92 (0.80, 1.07)	0.36	7.1	0.36
Quality score					
High quality studies (≥7)	5	0.89 (0.77, 1.02)	0.32	15.6	0.28
Adjustments					
Adjusted by oral contractive use	7	0.91 (0.82, 1.01)	0.39	5.4	0.60
Adjusted by hormone use	3	0.88 (0.77, 1.01)	0.27	22.7	0.40

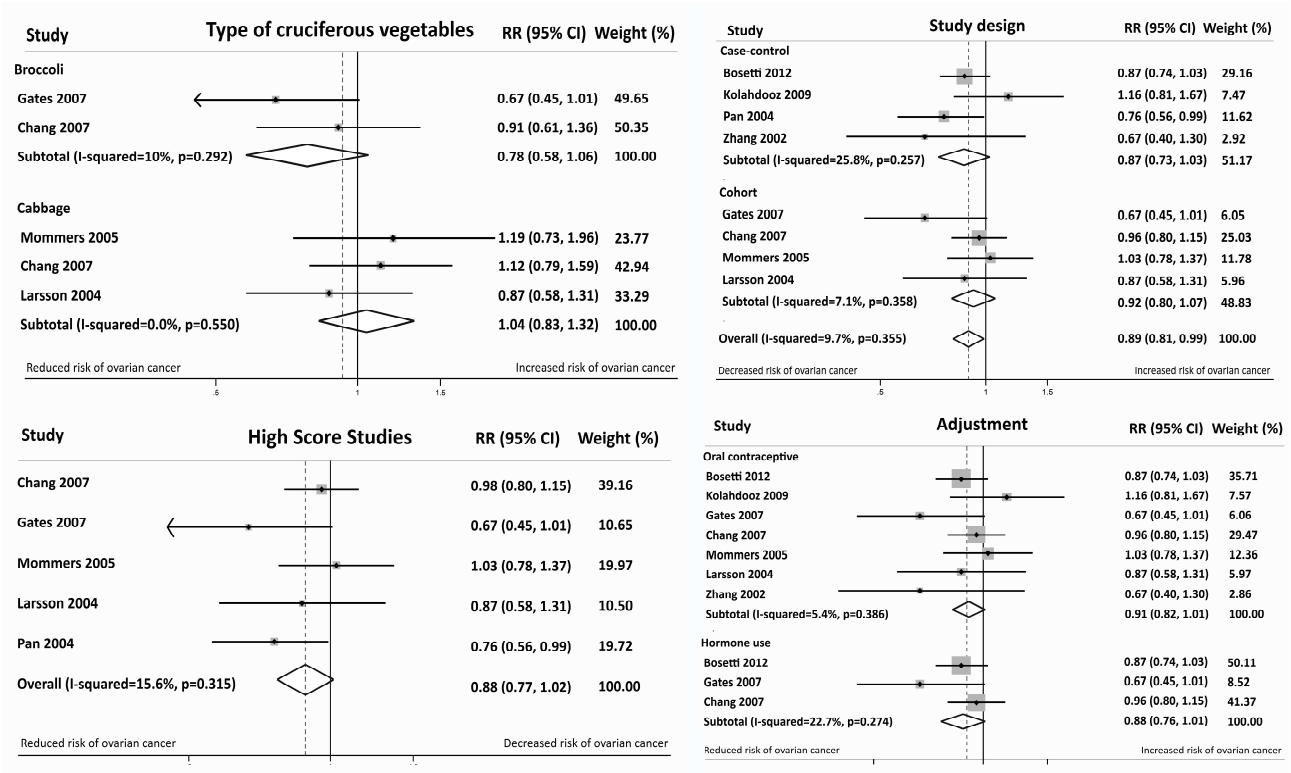

Figure 3. Forest plot of the subgroup analyses by CV type, study design, quality score and adjustments

analyses of case-controlled studies and cohort studies demonstrated similar results. Methodologically, the cohort studies were less prone to bias than the case-controlled studies. Thus, the reduction of the risk of ovarian cancer by CV consumption in case-controlled studies may have been magnified due to the nature of the study design.[15] To avoid bias caused by study design flaws, a subgroup analysis with only high-quality studies was performed, and a borderline significance was found. Similarly, a similar result with borderline significance was found with the two studies with quality scores of 6. Furthermore, oral contraceptive use and hormone use are two known risk factors for ovarian cancer. To exclude the influence of these two confounders, an analysis of studies with these two factors adjusted was performed. Both analyses suggested a reduced risk of ovarian cancer with marginal significance.

Our results, that CV consumption is associated with a reduced risk of ovarian cancer, can possibly be explained by previous studies investigating the anticancer effects of CV. These vegetables are a good dietary source of glucosinolates, which can produce isothiocyanates (ITCs) and indole-3-carbinol (I3C) after being hydrolyzed by myrosinase. ITCs inhibit the proliferation of ovarian cancer cells and induce apoptosis via the caspase-9 and -3 pathways.[35,36] I3C regulates the redox status of the cells during oxidative stress and protects ovarian cells from carcinogenesis.[37] Furthermore, I3C has synergic effects with bortezomib treatment on ovarian cancer cells.[38] These mechanisms contribute to the anticancer effects of glucosinolates and the by-products. However, to clearly elucidate the underlying mechanism so that the protective effects can be applied clinically, further investigations are necessary.

The major strength of this study was the large sample size (a total of 304432 subjects and 3301 cases), which provided sufficient power to reveal a reliable association between CV consumption and the risk of ovarian cancer.

In addition, the quality of the included studies was relatively high, since 5 out of 8 studies met the high quality criteria based on the 9-star NOS.

A number of limitations and pitfalls in our study should be identified. First, only studies published in English scientific journals were included in this meta-analysis. Because cruciferous vegetable consumption is considerably higher in Asian countries than elsewhere, the inclusion criteria may have excluded useful data published in Asian languages. Second, because the food frequency questionnaire (FFQ) was applied to assess the consumption of CV in all eight included studies, there could be measurement errors and/or ethnic differences. Third, the definition of CV consumption in the different publications was not standardized. More specifically, several studies compared the risk of ovarian cancer in the lowest and highest categories of CV consumption; however, the exact amount of CV consumed in the lowest and highest categories varied across the different studies. In addition, the preparation methods of CV, which was not adjusted for in most of the included studies, could considerably affect the final amount of bioactive compounds retained.[10,39] These detailed questions listed above will require hypothesis-specific clinical investigations.

In conclusion, this meta-analysis suggested that a high consumption of CV may reduce the risk of ovarian cancer. Despite the large sample sizes in the included investigations, the number of studies focusing on this association remains limited, especially for high quality cohort studies. Therefore, more high-quality studies in different regions with large sample sizes and well-balanced confounders are needed to confirm our findings. Further studies focused on the mechanisms of the preventative effect (s) are warranted for potential clinical application. In addition, most of the cancers with an inverse relationship with CV consumption were adenocarcinoma. Thus, it would be interesting to investigate whether pathology and histology play an important role in the protective effects of CV consumption.

AUTHOR DISCLOSURES

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Original Article

Intake of cruciferous vegetables is associated with reduced risk of ovarian cancer: a meta-analysis

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十字花科蔬菜的摄入可降低卵巢癌的发病风险：基于观察性研究的荟萃分析

背景：基于流行病学的研究显示，关于十字花科蔬菜的摄入是否能降低卵巢癌发生风险尚存在争议。本研究的目的是通过荟萃分析，探讨十字花科蔬菜摄入与卵巢癌的发生风险的相关性。**方法**：通过检索 Medline（Pubmed）、Embase 和 Web of science 数据库来查找相关研究（截止至 2013 年 10 月）。采用随机效应模型来计算整合的相对风险以及其 95%置信区间，并评价研究的异质性和发表偏倚。**结果**：符合入选标准的研究共有 8 项（4 项病例对照研究和 4 项队列研究）。通过分析发现，十字花科蔬菜高摄入相比于低摄入能显著降低卵巢癌的发生风险（RR：0.89；95% CI：0.81-0.99）。没有发现研究存在显著的异质性或发表偏倚。**结论**：本研究提示十字花科蔬菜高摄入可降低卵巢癌的发生风险，当然，十字花科蔬菜对卵巢癌的临床效果尚需进一步的研究来证实。

关键词：十字花科蔬菜、卵巢癌、流行病学研究、癌症预防、荟萃分析