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Original Article

Meta-analysis of the association between cruciferous vegetables intake and colorectal adenoma risk

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Abstract: Aim: Quantification of the association between intake of cruciferous vegetables (CV) and the risk of colorectal adenoma (CRA), and established precursors for colorectal cancer (CRC) remain unclear. We performed a meta-analysis of observational studies to explore this relationship. Methods: We identified studies by a literature search of MEDLINE and EMBASE from inception through to November 30, 2015, and by searching the reference lists of pertinent articles. We calculated summary relative risks (SRRs) with corresponding 95% confidence intervals (CIs) using a random-effects model. Results: We identified 11 observational studies involving a total 8,030 cases of CRA. Overall, the SRR for high CV intake on CRA risk was 0.86 (95% CI 0.75-0.98). There was evident heterogeneity among the included studies (I^2 = 44.8%, $P_{heterogeneity}$ = 0.046). When analyzed separately, case-control studies yielded statistically significant results (SRR = 0.77, 95% CI 0.62-0.96), while the results of prospective studies showed no statistical significance (SRR = 0.96, 95% CI 0.87-1.06). The reduced risk of CRA with CV intake was significant in European studies, although it was not significant in American studies. Dose-response analysis found a marginally significant inverse association (per serving per week; SRR = 0.96, 95% CI 0.92-1.00). Conclusions: Our results indicate that CV intake may be associated with reduced risk of CRA. More research on specific CV, food preparation methods, and adjustment for potential confounders should be performed in the future.

Keywords: Colorectal adenoma, cruciferous vegetables, meta-analysis, relative risk

Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and the second most common cause of cancer death in North America [1]. Epidemiological studies have suggested that dietary factors contribute to the etiology of CRC, but only alcohol abuse in men and the consumption of red and processed meat have been clearly identified as risk factors for this deadly disease [2]. Colorectal adenoma (CRA) is thought to be a potential precursor of CRC, although some evidence has indicated that CRC can also originate de novo [3]. Accordingly, it is reasonable to believe that adenoma and carcinoma have a common etiology. Currently, it has been reported that some environmental factors, including smoking [4], and obesity [5] and some dietary factors [6, 7] play an essential role in the development of CRA.

Cruciferous vegetables (CV), a group of vegetables named for their cross-shaped flowers, include broccoli, Brussels sprouts, cabbage, cauliflower, collards, kale, and kohlrabi. Like other vegetables, CV contain many substances, such as vitamin C, vitamin E, folate, carotenoids, and flavonoids, which are believed to prevent the formation of nitrosamines, induce detoxifying phase II enzymes, and promote apoptosis [8, 9]. Furthermore, CV are unique because they are rich sources of glucosinolates, a sulfur-containing compound [10, 11]. The enzyme myrosinase hydrolyzes glucosinolates into the biologically active compound isothiocyanate (ICT), which may help prevent cancer by inhibiting carcinogen-activating enzymes, detoxifying carcinogens, inducing apoptosis, and arresting cell cycle progression [2, 9, 12].

Recently, observational studies have indicated that the intake of CV plays a potential protective role against the development of lung, colorectal, stomach, breast, and renal cell carcinoma [13-16]. With regard to the association between CV intake and CRA, a body of observational studies has examined this association and

reported inconsistent results [17-27]. Where some studies did not observe significant effects [18-26], others described significantly reduced CRA risk [1, 2]. Therefore, to better characterize this issue, we conducted a meta-analysis of all published studies to evaluate the relationship between CV intake and CRA risk.

Methods

Literature search

Two investigators (C.R. and D.Q.J.) identified the published literature in the EMBASE and MEDLINE databases from inception to November 30, 2015. Additional articles were also retrieved with a manual search of the reference lists in the pertinent articles. For the database search, the following keywords or MeSH terms were used: (1) cruciferous OR vegetables OR fruits OR brassica OR broccoli OR cauliflower OR cabbage, (2) adenoma OR polyp, and (3) colon OR rectal OR colorectal OR large bowel. This meta-analysis was planned, conducted, and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [28]. No language restriction was applied.

Study selection

To include an article according to the general inclusion criteria, two researchers (C.R. and D.Q.J.) independently reviewed all retrieved articles. The eligibility criteria included: (1) a cohort or case-control design; (2) availability of odds ratio (OR) or relative risk (RR) and its 95% confidence intervals (CI) in each article, or raw information allowing us to compute them; and (3) associations at least adjusted or matched by age. Rejected formats included non-peer-reviewed articles, animal studies, in vitro studies, ecologic assessments, correlation studies, and cross-sectional studies. If data were duplicated in more than one study, we included the most recent or informative study. Disagreement was resolved by discussion.

Data extraction

C.R. and D.Q.J. performed the data extraction; a data extraction form was designed for recording the relevant information: study design, the first author, publication year, location, number of cases and controls or participants, collection methods of data on dietary exposure, confounders, and OR or RR. From each study, we extracted the risk estimates controlled for the greatest number of potential confounders.

Quality assessment of individual studies

To evaluate study quality, C.R. and D.Q.J. used the Newcastle-Ottawa Scale (NOS) [29], which uses three quality parameters for case-control/cohort studies: selection (maximum points = 4), comparability (maximum points = 2), and exposure/outcome assessment (maximum points = 3). The maximum total score is 9, with a score ≥ 7 indicating high study quality.

Statistical analysis

Data analysis was performed using a random-effects model to calculate summary RRs (SRRs) (95% CIs), which accounts for heterogeneity among studies [3]. For one study [1] that did not report the 95% CI, we estimated the crude RR (95% CI) for the highest vs. lowest level using dietary exposure distributions. A two-tailed *P*-value < 0.05 was considered significant. The STATA statistical package version 11.0 (STATA, College Station, TX, USA) was used for all data analyses.

Assessment of heterogeneity among studies was carried out using both the Q statistic and I^2. Statistically significant heterogeneity existed if the *P*-value < 0.10. For the I^2, which assesses the percentage of variability in the effect estimates due to heterogeneity rather than chance, a value > 50% indicated substantial heterogeneity [31]. Explanations for the observed heterogeneity must be sought using subgroup and random-effects meta-regression analyses. To investigate the influence of each individual study on the summary risk estimations, we conducted sensitivity analysis by repeating the random-effects meta-analyses, omitting one study at a time.

Whenever possible, we carried out line dose-response meta-analyses using generalized least-squares trend estimation (GLST) [4, 5]. For each category of intake level, the medians were assigned to corresponding risk estimations. If medians were unavailable, we assigned them in each category by calculating the average of the lower and upper boundaries. When the lowest category was open-ended, the lowest boundary was considered zero. When the highest category was open-ended, it was

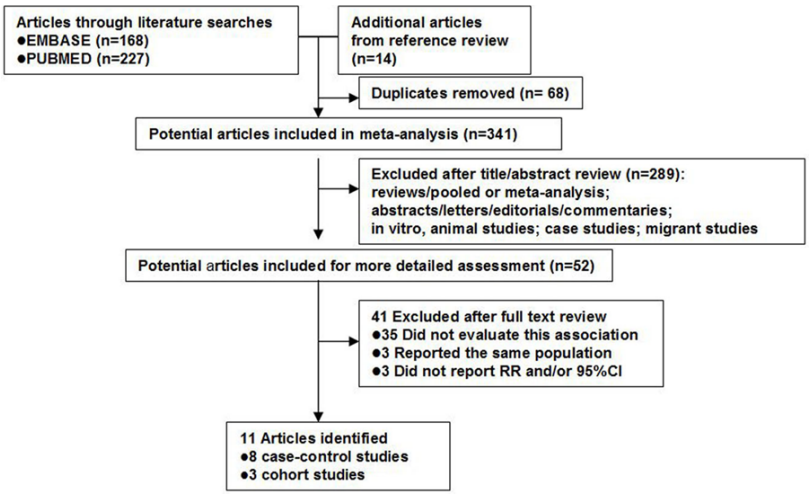

Figure 1. Flow diagram of systematic literature search on cruciferous vegetables intake and the risk of colorectal adenoma.

assumed that the open-ended interval length was equal to the adjacent interval. The dose-response results are presented as per serving per week increments in CV consumption.

Publication bias was assessed using funnel plots and further with Begg's adjusted rank correlation and Egger's regression asymmetry test [6, 7].

Results

Search results and study characteristics

As shown in **Figure 1**, we identified 395 potentially relevant citations. Scanning reference lists and personal databases identified 14 additional articles. Of these 409 articles, 52 were considered of potential value and the full text was retrieved for detailed evaluation. Forty-one of these 51 articles were subsequently excluded from the meta-analysis (35 articles did not assess the studied association, three reported the same population, and three did not report RR and/or 95% CI). Hence, 11 articles, i.e., three cohort and eight case-control studies, were included in this meta-analysis.

The characteristics of these studies are presented in **Table 1**. Of these 11 articles, seven were from America and the remaining four were from Europe. A total 8,030 subjects with CRA were involved. One study [8] presented risk estimations separately for women and men. Two studies [9, 10] investigated CV intake and CRA risk only in male or female populations. Most of the studies used RRs controlled for tobacco smoking, body mass index (BMI), and total energy intake. About half of the studies used RR estimates controlled for alcohol use and physical activity.

As shown in Supplementary Table 1, the quality scores ranged from 6 to 9, with a median score of 8. The majority of the included studies (10/11) were of high quality (NOS score ≥ 7).

High vs. low analysis

As there was significant heterogeneity (I^2 = 44.8%, $P_{heterogeneity}$ = 0.046), the random-effects model was used instead of a fixed-effects model. High CV consumption played a protective role against CRA development (SRR = 0.86, 95% CI 0.75-0.98, **Figure 2A**).

Dose-response analysis

Six studies [8, 10-13] were included in the dose-response analysis of CRA risk per serving per week increase in CV intake in a random-effects model, and a marginally significant inverse association was found (SRR = 0.96, 95% CI 0.92-1.00), with evident heterogeneity across studies ($P_{heterogeneity}$ < 0.001, I^2 = 75.3%; **Figure 2B**).

Subgroup and sensitivity analyses

Subgroup analyses for the association between CV intake with CRA risk are shown in **Table 2**. Statistically significant protective effects of CV intake against CRA were observed among case-control studies (SRR = 0.77, 95% CI 0.62-0.96; I^2 = 50.1%, $P_{heterogeneity}$ = 0.042) but not among cohort studies (SRR = 0.96, 95% CI 0.87-1.06; I^2 = 0%, $P_{heterogeneity}$ = 0.764). When stratifying analyses by population, CV consumption was significantly correlated with decreased CRA risk among the European studies (SRR = 0.58, 95% CI 0.43-0.77); however, no significant association was observed among the American studies (SRR = 0.94, 95% CI 0.85-1.04). Excluding one study [1] with a low quality score, we found borderline significant risk association (SRR = 0.88, 95% CI 0.78-1.00). In addition, adjusting for

Table 1. Characteristics of studies of cruciferous vegetables intake and colorectal adenoma risk

Author/year	Country	Number of cases sex	Number of controls/ participants	Dietary assessments	Contrast (Highest vs. lowest)	RR (95% CI) (Highest vs. lowest)	Adjustments
Case-control							
Benito/1993 [1]	Spain	101 CRA M+F	242 polyp-free	FFQ-99, Not available	Q4 vs. Q1	0.56 (0.34-0.92)	Age, sex
Witte/1996 [11]	USA	529 CRA M+F	563 polyp-free	Validated FFQ	7.0 vs. 0.5 servings/wk	0.67 (0.41-1.09)	Age, race, BMI, physical activity, smoking, calories, and saturated fat dietary fiber, folate, beta-carotene, and vitamin C
Lin/1998 [12]	USA	114 CRA M+F	116 polyp-free	Validated FFQ-126	7.8 vs. 0.6 servings/wk	0.66 (0.44-1.0)	Age, sex, smoking, saturated fat, energy intake, intake of fruits and vegetable
Almendingen/2001 [33]	Norway	87 CRA, M+F	35 polyp-free	5-day dietary record	> 60 vs. < 6 g/day	0.3 (0.1-1.1)	Age, sex, BMI, tobacco use, energy, fat, fiber and FHC
Breuer-Katschinski/2001 [34]	German	184 CRA M+F	178 polyp-free	Validated FFQ-126	Q5 vs. Q1	0.71 (0.37–.137)	Age, sex, energy, relative weight and social class
Smith-Warner/2002 [8]	USA	564 CRA M+F	682 polyp-free	Validated FFQ-153	6.7 vs. 1.0 4.7 vs. 0.6 servings/wk	1.39 (0.89-2.19) F 1.00 (0.64-1.54) M	Age, energy intake, fat intake, BMI, smoking status, alcohol status, NSAID, multivitamin use, and hormone replacement therapy use
Wu/2009 [35]	USA	764 CRA M+F	1517 Polyp-free	Validated FFQ-108	T3 vs. T1	0.94 (0.73–1.20)	Age, sex, race, study location, BMI, smoking status, alcohol, NSAID use, physical exercise, education level, family income, FHC, and red/processed meat intake in addition to total energy intake
Northwood/2010 [2]	UK	317 CRA M+F	296 Polyp-free	Validated FFQ	> 11.4 vs. < 3 servings/ month	0.59 (0.37–0.93)	Age, sex and smoking
Cohort							
Platz/1997/ [9]	USA	HPFS 690 CRA M	N = 16,448	Validated FFQ-131	2.2 vs.0.3 g/day	0.96 (0.71-1.31)	Age, endoscopy, FHC, BMI, smoking, multivitamin use, physical activity, aspirin use, energy, alcohol, red meat, folate, and methionine.
Michel/2006 [10]	USA	NHS n = 1720 CRA F	N = 34,467	Validated FFQ-131	> 1 serving/d vs. < 1 serving/wk	0.90 (0.75-1.10)	Age, FHC, BMI, vigorous exercise, aspirin use, smoking, current multivitamin supplement use, alcohol consumption, total caloric intake, red meat consumption, calcium intake, menopausal status, and postmenopausal hormone use
Millen/2007 [13]	USA	PLCO n = 3057 CRA M+F	N = 29,413	Validated FFQ-137	1.0 vs. 0.1 servings/day	0.98 (0.86-1.10)	Age, sex, study center, race, education, FHC, smoking, alcohol use, use of ibuprofen, use of aspirin, use of replacement hormones, physical activity, BMI

Abbreviation: CRA, colorectal adenoma; NSAID, nonsteroid anti-inflammatory drugs; FHC, family history of colorectal cancer; M, male; F, female; FFQ, Food Frequency Questionnaire; BMI, body mass index; NHS, Nurses' Health Study; PLCO, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; HPFS, Professionals Follow-up Study.

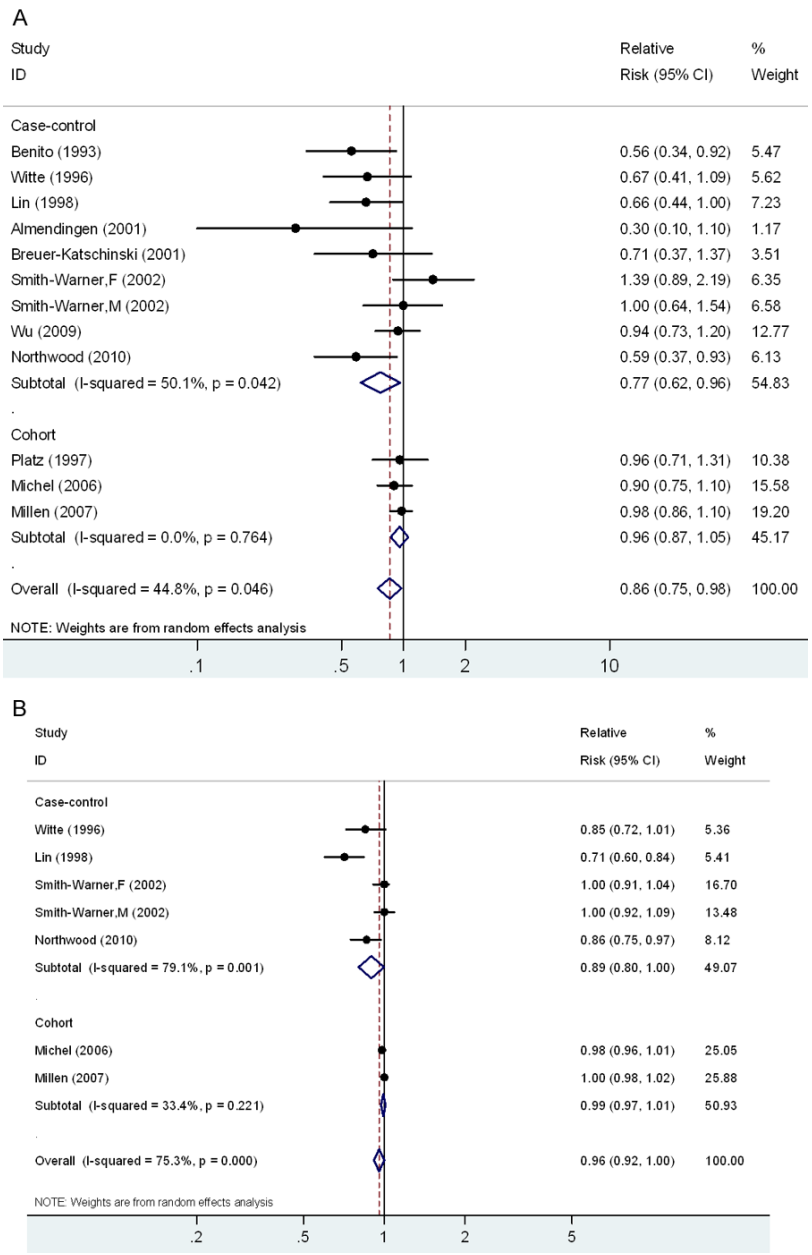

Figure 2. Forrest plots for the association between cruciferous vegetables intake and the risk of colorectal adenoma. A. High *vs*. low analysis; B. Dose-response analysis (per 1 serving/week).

BMI and alcohol use significantly attenuated the association between CV intake and CRA risk, and this risk association was not statistically significant again. Adjusting for smoking, total energy intake, and physical activity did not change this association, and it remained statistically not significant.

Sensitivity analyses, which were carried out by excluding one study at a time, showed no significant variation in the combined risk estimations, confirming the robustness of the present results.

Meta-regression analysis

We carried out meta-regression analysis to better explore the possible sources of inter-study heterogeneity. As shown in **Table 2**, univariate meta-regression analysis indicated that geographic location (Europe vs. America, P = 0.01) and major confounders adjusted by alcohol intake (yes vs. no, P = 0.009) or by BMI (yes vs. no, P = 0.003) may be potential sources of heterogeneity. In multivariate meta-regression analysis, only confounders adjusted by BMI were statistically significant (P = 0.091).

Publication bias

There was no indication of publication bias for studies on the association between CV intake and CRA risk, with P = 0.115 for Begg's test (**Figure 3**) and 0.366 for Egger's test.

Discussion

The present meta-analysis assessed the relationship between CV intake and CRA risk in an overall sample of 8,030 CRA cases from eight case-control and three cohort studies. The main findings support the evidence for a reduced risk relationship between CV intake and CRA risk. The risk decrease estimated for the highest vs. lowest intake was 14%, which was significant in the European and case-control studies but not so in the American and cohort studies.

The results from the present meta-analysis revealed a statistically significant inverse association among case-control studies but a non-

Table 2. Subgroup analyses of cruciferous vegetables intake and colorectal adenoma risk

Sub-groups	Studies, n	SRR (95% CI)	Q	P_h*	I^2 (%)	P_d**
All	11	0.86 (0.75-0.98)	19.92	0.046	44.8	
Design						0.232
Cohort	3	0.96 (0.87-1.06)	0.54	0.764	0	
Case-control	8	0.77 (0.62-0.96)	16.04	0.042	50.1	
Geographic locations						0.010
Europe	4	0.58 (0.43-0.77)	1.55	0.670	0	
USA	7	0.94 (0.85-1.04)	8.32	0.305	15.9	
FFQ						0.166
Validated	10	0.88 (0.78-0.99)	16.19	0.094	38.2	
Non-calidated	1	0.56 (0.34-0.92)	-	-	-	
Study quality score						
High (NOS score > 6)	10	0.88 (0.78-1.00)	16.19	0.094	38.2	0.166
Low (NOS score ≤ 6)	1	0.56 (0.34-0.92)	-	-	-	
Adjustments						
BMI, Yes	7	0.95 (0.85-1.06)	8.87	0.262	21.1	0.009
No	4	0.62 (0.49-0.79)	0.46	0.928	0	
Smoking, Yes	9	0.89 (0.78-1.02)	15.58	0.076	42.2	0.147
No	2	0.61 (0.41-0.91)	0.32	0.572	0	
Alcohol use, Yes	5	0.97 (0.89-1.06)	3.15	0.677	0	0.003
No	6	0.62 (0.50-0.76)	1.96	0.855	0	
Dietary energy intake, Yes	8	0.89 (0.76-1.03)	11.41	0.180	29.9	0.513
No	3	0.72 (0.47-1.11)	8.40	0.015	76.2	
Physical activity, Yes	5	0.94 (0.86-1.03)	2.50	0.646	0	0.167
No	6	0.74 (0.55-1.00)	13.80	0.032	56.5	

Abbreviation: FFQ, Food Frequency Questionnaire; BMI, body mass index; NOS, Newcastle-Ottawa Scale. *, P_h value tests among-study heterogeneity. **, P_d value tests between-subgroup heterogeneity.

significant inverse association among cohort studies. In the case-control studies, exposure information was available after the disease diagnosis, therefore it may have been subject to recall bias and inaccurate measurement of CV intake, which may have inflated the SRRs. In two cohort studies [10, 13], CV intake was assessed only once at baseline, although the other cohort (HPFS) updated exposure and disease information biennially by mail [9]. Therefore, the overall findings of reduction in CRA risk should not be overemphasized.

The results from the present meta-analysis revealed a significant reduction in CRA risk in European populations, but not in American ones. The reasons for this discrepancy are unclear. However, discrepancies in culture, genetic susceptibility, and lifestyles may partially address the question. For example, it is indicated that genetic variants may affect the effects of CV consumption on cancer risk. Glutathione-S-transferase (GST), a phase II conjugating enzyme, can conjugate ICTs, leading to excretion. The results from the prospective Singapore Chinese Health Study reported that intake of ICTs from CV might modify CRC risk in individuals with low GST activity, suggesting an interaction between ICT consumption and GST variants [14]. In addition, food preparation methods are different between European and American populations, which may influence the exposure levels of ICTs [15]. For example, a 30%-60% loss of intact glucosinolates due to thermal degradation and leaching was observed when boiling CV [16]. However, none of the studies separated the CV intake by cooking method. Therefore, future epidemiological studies should consider whether the inverse association of CV intake and CRA risk is affected by the food preparation method and susceptibility genes, which may play an important role in the metabolism of CV.

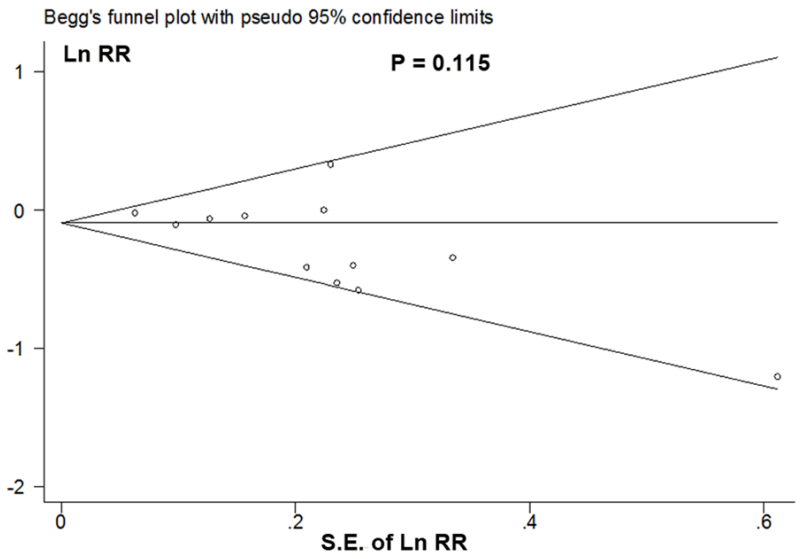

Figure 3. Begg's funnel plots of the log relative risks (RRs) versus the SEs of the log RRs in studies that evaluated the effect of cruciferous vegetables intakes on the risk of colorectal adenoma.

Several laboratory studies might explain the inverse association between CV intake and cancers. In addition to the cancer-protective properties as in other vegetables, such as vitamin C, vitamin E, folate, carotenoids, and flavonoids, CV are unique in that they are rich sources of glucosinolates [17, 18], the precursors of ICTs and indole-3-carbinol [19, 20]. ICTs may help prevent cancer with multifaceted mechanisms, including the inhibition of carcinogen-activating enzymes, detoxification of carcinogens, induction of apoptosis, and arrest of cell cycle progression [15, 20, 21]. Furthermore, animal studies have shown that CV might inhibit colorectal carcinogenesis induced by chemical carcinogens [22, 23]. In addition, CV are good sources of fiber, which are protective against colorectal carcinogenesis by several plausible mechanisms, including increased fecal bulk, reduced stool transit time, and increased short-chain fatty acids formation by dietary fiber fermentation [41, 42].

The meta-analysis presented here has several strengths. This is the first comprehensive meta-analysis focusing on the association between CV intake and CRA risk, and it included several prospective studies, included only outcome as the precursor for CRC (i.e., CRA), used linear meta-analytic methods, and conducted several subgroup analyses. Its additional strengths are its extensive literature search and examination of the retrieved materials by at least two co-authors.

As a meta-analysis of observational studies, our findings have several limitations. Measurement errors are important in the assessment of dietary intake, which can distort the relationship between dietary intake and cancer risk [24, 25]. Measurement errors may occur, because eight of the 11 studies included in this meta-analysis were based on a case-control design, which is more susceptible to recall biases, especially dietary recall bias, than a cohort design. Inaccurate measurement of CV intake might occur when using a non-validated questionnaire to assess CV intake. However, only one study did not use a validated food frequency questionnaire (FFQ) to evaluate CV consumption, and excluding this study did not significantly change the risk association. Measurement error can also occur if results based on different intake units are reported (such as servings per day or per week; grams per day; and tertiles, quartiles, or quintiles of consumption without demarcating the cutoff points of exposure). In addition, it is very difficult for people to accurately report their intake of vegetables, including CV. Previous validated studies have shown relatively low correlations, with correlation coefficients of 0.4 for vegetable consumption [26, 27], which may lead to the attenuation of risk estimates.

The results of the current meta-analysis indicated significant heterogeneity across studies, which may reflect differences in population, study design, location, dietary exposure assessment, dietary intake category, and confounding factors used for adjustment. We used a random-effects model, and not a fixed-effects model, as the former provides a more conservative standard error and a larger CI than the latter in determining SRRs. Furthermore, we carried out meta-regression analyses to investigate possible sources of heterogeneity. Univariate meta-regression analyses found that

geographic location and confounding factors controlled for alcohol use and BMI were possible sources of inter-study heterogeneity. Multivariate meta-regression analyses found that confounding factors adjusted by BMI might partially account for the significant heterogeneity across studies.

As for the observational nature of the data, it is possible that the observed significant inverse association between CV intake and CRA risk could have been due to unmeasured or residual confounding. Individuals who consume more vegetables may also have generally "healthier" dietary and lifestyle patterns, such as lower prevalence of tobacco smoking and overweight/obesity, drinking less alcohol, and being physically active [28, 29]. Furthermore, adjustment for total energy intake is important when accounting for the potential confounding factors in nutritional studies [30]. However, the subgroup analyses according to the above confounding factors (physical activity, smoking, and total energy intake) found similar risk estimations.

We found that adjustment for BMI was a possible residual confounding factor after performing the multivariate meta-regression analyses. Several interventional trials [31, 32] have reported the protective role of vegetable intake against weight gain. The present meta-analysis found that the association between CV intake and CRA risk was significantly stronger when the results were not adjusted by BMI than those with adjustment for BMI (RR = 0.62 vs. 0.95, respectively). Therefore, reduced body fat may explain part, but not all, of the protective effect of CV against CRA risk.

As in any meta-analysis, the possibility of publication bias was of concern because small studies with negative results tend not to be published, although the results obtained from funnel plot and statistical tests did not provide evidence for such bias.

In summary, this meta-analysis suggests that high CV intake might lead to a significantly lower risk of CRA. Further studies are needed to present more detailed results, including specific types of CV, different methods of food preparation, and the interaction between ICTs and genetic variants in the metabolism of CV.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Quality assessment according to the Newcastle-Ottawa scale

	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Controls for age	Controls for other	Assessment of outcome	Follow-up	Adequacy of follow up	Score
Cohort										
Platz/1997	0	1	1	1	1	1	1	1	1	8
Michel/2006	0	1	1	1	1	1	1	1	1	8
Millen/2007	1	1	1	1	1	1	1	0	1	8
	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	Controls for age	Controls for other	Ascertainment of exposure	Same method	Non-Re-sponse rate	
Case-control										
Benito/1993	1	1	1	0	1	0	1	1	0	6
Witte/1996	1	1	0	1	1	1	1	1	1	8
Lin/1998	1	1	0	1	1	1	1	1	1	8
Hoshiyama/2000	1	1	0	1	1	0	1	1	1	7
Almendingen/2011	1	1	1	1	1	1	1	1	0	8
Breuer-katschinsk/2001	1	1	0	1	1	1	1	1	1	8
Smith-Warner/2002	1	1	1	1	1	1	1	1	0	8
Wu/2009	1	1	1	1	1	1	1	1	1	9
Northwood/2010	1	1	1	1	1	0	0	1	1	7