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Original article

Cruciferous vegetables intake is inversely associated with risk of breast cancer: A meta-analysis

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ABSTRACT

Purpose: The objective of the study was to examine the associations of cruciferous vegetables intake with risk of breast cancer.

Methods: Studies were identified by searching PubMed databases and screening the references of retrieved articles and reviews. Summary odds ratios (ORs) for the highest *versus* lowest cruciferous vegetables consumption levels were calculated using fixed or random effects models depending on heterogeneity between studies. Heterogeneity among studies was examined using Q and I^2 statistics. Publication bias was assessed using the Egger's and Begg's tests.

Results: Thirteen epidemiologic studies (11 case-control and 2 cohort studies) were included in the meta-analysis. The combined results from all studies indicated that high cruciferous vegetables intake was significantly associated with reduced breast cancer risk (RR = 0.85, 95% CI = 0.77–0.94).

Conclusion: Findings from this meta-analysis suggest that cruciferous vegetables consumption may reduce the risk of breast cancer. Because of the limited number of studies, further prospective studies are needed to explore the protective effect of cruciferous vegetables on breast cancer.

Introduction

Breast cancer ranks as the most common cancer and the first major cause of cancer death among women in the world, with an expected 1,383,500 newly diagnosed cases and 458,400 deaths in 2010.[1] The incidence of breast cancer varies about five-fold among populations around the world,[2] and the rates increase after a woman migrates from low-risk to high-risk countries,[3] suggesting that breast cancer is possibly preventable. Reproductive factors such as low parity and late age at first birth are well-known risk factors for breast cancer. Dietary factors in the cause of breast cancer have been of great interest and extensively investigated during the last decades.[4]

Increasing vegetable consumption has been widely recommended as a key component of a healthy diet to reduce the risk of major chronic diseases such as cancer. However, the role of vegetable consumption in relation to breast cancer risk is controversial. A meta-analysis of 14 case-control and 3 cohort studies reported that breast cancer risk was reduced by 25% due to the high vegetables intake,[5] whereas a pooled analysis of 8 cohort studies found that vegetable consumption might be not significantly associated with reduced breast cancer risk.[6] The relationship between consumption of certain subcategories of vegetables and breast cancer risk remains unclear. Cruciferous vegetables are a special group of vegetables named for their cross-shaped flower petals, including cabbage, broccoli, brussels sprouts, cauliflower, and other members of the family. There is accumulating evidence that cruciferous vegetable consumption may lower the risk for several types of cancers.[7] Although several epidemiological studies have focused on the association between cruciferous vegetable intake and breast cancer risk, their conclusions have been inconsistent. We therefore conducted a meta-analysis of all published studies to gain a better understanding of the relationship between them.

Materials and methods

Literature research

We identified studies by a literature search using PubMed database, covering the period up to November 2011, under the terms "cruciferous vegetable*" or "brassica", "breast cancer", and "risk" as text words. The titles and abstracts of studies were firstly scanned to exclude all irrelevant papers, and then we determined the final studies included by reading the full text of the remaining articles. In addition, the electronic searches were supplemented by scanning the reference lists from retrieved articles to identify additional studies.

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Study selection

We searched for case-control and cohort studies that assessed cruciferous vegetables consumption in relation to breast cancer. Cross-sectional and ecologic analyses were excluded, as were studies without informative effect estimates. In studies with overlapping patients or controls, the latest study with the largest sample size was included.

Data extraction

Two authors independently extracted data from each eligible study as follows: the name of the first author, the year of publication, the country in which the study was conducted, study design, study period, sample size, effect estimates for highest *versus* lowest level of consumption, exposure assessment and adjusted covariates. Considering that breast cancer is a rare disease, the RR was assumed approximately the same as OR, and the OR was used as the study outcome. For studies that reported several multivariable-adjusted ORs, we extracted the maximally adjusted ones. Two studies[8,9] reported separate OR for premenopausal and postmenopausal women but no overall OR, we calculated it by combining these estimates with the method of Mantel and Haenszel.[10]

Statistical analysis

In our meta-analysis, we pooled data using the fixed or random effects models depending on heterogeneity between studies. We also conducted separate subgroup analyses of breast cancer incidence by menopausal status, study design, geographical region, and exposure assessment. Publication bias was assessed using the tests of Egger[11] and Begg.[12] Statistical significance was considered while $p < 0.05$. We performed all statistical analyses with Stata v.11.0 (StataCorp, College Station, TX).

Results

The process of study selection was shown in Fig. 1. The primary literature search identified 53 records. After screening the titles and abstracts, 41 articles were excluded because they were either laboratory studies, review articles, or irrelevant to the current study. In total, 12 papers were retrieved and reviewed by 2 authors.[13–24] One study by Thomson et al.[14] was excluded because they only evaluated the association of cruciferous vegetables consumption with recurrence of breast cancer. Four studies were excluded because of insufficient information to compute its relative risk (RR) or odds ratio (OR) and 95% confidence intervals (CI).[15,16,19,20] One case-control study published results in two different articles,[18,22] and we excluded the study by Fowke et al.[22] because of relative small sample size. In addition, we included seven studies after reviewing reference lists of retrieved articles or preceding reviews.[8,9,25–29] Finally, a total of 13 studies were retrieved for the meta-analysis, including a total of 18,673 cases (Table 1).

Of the selected 13 studies, three were hospital-based case-control,[12,17,19,24,25,29] and eight population-based case-control studies.[8,18,21,23,25–28] Only two cohort studies were included.[9,13] Eight of these studies were conducted in the United States,[8,9,13,21,24–27] while 3 were in China[17,18,28] and 2 in Europe.[18,23,25,29] Information on cruciferous consumption was obtained by interview[8,17,18,21,23,25–29] and mailed questionnaire.[9,13,23] Seven studies[8,9,13,18,21,23,27] provided ORs for postmenopausal women and five studies[8,9,13,18,21] for premenopausal women.

In Fig. 2 we presented the overall ORs of breast cancer comparing the highest *versus* the lowest cruciferous consumption categories. When all these studies were analyzed together, we observed a statistically significant 15% reduced risk of breast cancer (OR = 0.85; 95% CI = 0.77–0.94). There was significant heterogeneity among the studies ($p = 0.017$). However, after excluding one study by Zhang et al.,[17] which reported a considerable inverse association, the results were homogenous (OR = 0.90; 95% CI = 0.85–0.96; $p = 0.464$). Fig. 3 depicts a Begg's funnel plot of included studies, indicating that there was no publication bias. Further, there was no evidence of publication bias using Egger's test ($p = 0.77$).

In Table 2, we assessed associations separately for menopausal status, studies design, geographical region, and cruciferous vegetables assessment. The OR estimates varied little by study design and exposure assessment, showing that cruciferous vegetables consumption was consistently associated

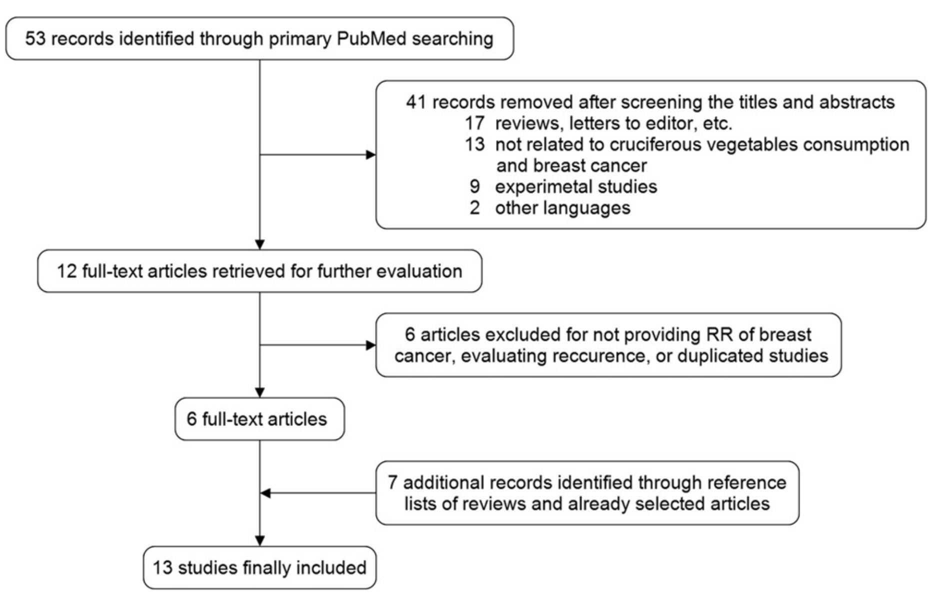

Fig. 1. Process of study selection for cruciferous vegetables consumption and risk of breast cancer.

Table 1
Study characteristics of published cohort and case-control studies on cruciferous vegetables intake and breast cancer.

Authors	Publication year	Study design	Study period	Country	Cases/Subjects	Variables of adjustment	Cruciferous vegetables assessment
Graham et at	1982	Hospital-based case-control study	1958–1965	USA	2024/3487	None.	Interview
Franceschi et al.	1998	Hospital-based case-control study	1991–1996	Italy	2569/5155	Age, center, year of interview, education, physical activity, alcohol and energy intake, and parity.	Interview
Zhang et al.	1999	Cohort	1980–1994	USA	2679/83,234	Age, length of follow-up, total energy intake, parity, age at first birth, age at menarche, history of breast cancer in mother or a sister, history of benign breast disease, alcohol intake, body mass index at age 18 years, weight change from age 18 years, and height in inches.	Questionnaire
Potischman et al.	1999	Population-based case-control study	1990–1992	USA	568/2019	Age at diagnosis, study site, ethnicity, education, age at first birth, alcohol intake, years of oral contraceptive use and smoking status.	Interview
Rosenblatt et al.	1999	Population-based case-control study	1983–1986	USA	220/511	Caloric intake	Interview
Terry et al.	2001	Population-based case-control study	1993–1995	Sweden	2832/5482	Age, height and body mass index, current smoking, socioeconomic status, consumption of alcohol, consumption of high-fiber grains and cereals, consumption of fatty fish, multivitamin use, parity, hormone replacement therapy, history of benign breast disease, family history of breast cancer, type of menopause, age at menopause, age at menarche, and age at first birth.	Questionnaire
Shannon et al.	2003	Population-based case-control study	1988–1990	USA	441/811	Age, total energy intake, number of pregnancies, and highest level of education.	Interview
Gaudet et al.	2004	Population-based case-control study	1996–1997	USA	1463/2963	Age and energy.	Interview
Ambrosone et al.	2004	Population-based case-control study	1986–1991	USA	740/1650	Age, education, age at menarche, age at first pregnancy, family history of breast cancer, BMI, and age at menopause for postmenopausal women.	Interview
Shannon et al.	2005	Population-based case-control study	1995–1997	China	378/1448	Age, total fruit and vegetable intake, and breast-feeding.	Interview
Lee et al.	2008	Population-based case-control study	1996–1998, 2002–2005	China	3035/6072	Age, education, age at menarche, age at live birth, BMI, family history of breast cancer, regular exercise, total energy intake, and study phase.	Interview
Zhang et al.	2009	Hospital-based case-control study	2007–2008	China	438/876	Age at menarche, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking, and total energy intake.	Interview
Boggs et al.	2010	Cohort	1995–2007	USA	1268/51,928	Age, energy intake, age at menarche, body mass index at age 18 years, family history of breast cancer, education, geographic region, parity, age at first birth, oral contraceptive use, menopausal status, age at menopause, menopausal hormone use, vigorous activity, smoking status, alcohol intake, and multivitamin use.	Questionnaire

with a decreased risk of breast cancer. The inverse association in China, although nonsignificant, seems to be greater than that in US and Europe. We found that consumption of cruciferous vegetables was associated with a reduced risk of post-menopausal breast cancer, whereas significant risk reduction was not noted for premenopausal women.

Discussion

This present meta-analysis summarized the evidence to date regarding the association between cruciferous vegetables consumption and breast cancer risk, representing a pooled total of 18,673 cases. We have found that cruciferous vegetables consumption was significantly associated with reduced risk of breast cancer. This finding is inconsistent with the previous pooled analysis 8 cohort studies by Smith-Warner et al.,[6] which did not observe strong or statistically significant for any of the fruit and vegetable groups or items examined, including cruciferous vegetables (RR = 0.96, 95% CI = 0.87–1.06). In the present meta-analysis, most of the studies were case-control, which have the potential for recall bias because individuals with breast cancer may associate their malignancy with a previous "bad diet" and thus overreport foods considered less healthy. However, these studies are consistent in one sense because cruciferous vegetables have not been associated with increased breast cancer risk, and the two prospective studies also offer a significant reduced risk in subgroup analysis (RR = 0.86, 95% CI = 0.72–0.99), underscoring the independent negative association of cruciferous vegetables consumption with breast cancer.

Cruciferous vegetables consumption levels are high and consumed with great frequency in China. In separate analysis by geographical region, the relatively lower summary OR in china, albeit not statistically significant, suggests a dose–response relationship between cruciferous vegetables intake and risk of breast cancer, although this analysis could not be performed due to lack of data. We also found significantly reduced risk for intake of cruciferous vegetables among postmenopausal

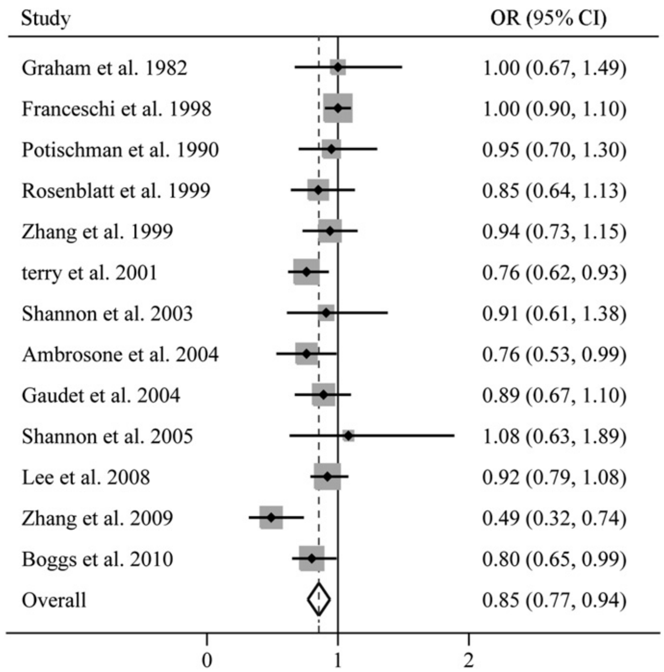

Fig. 2. A forest plot showing risk estimates from case-control and cohort studies estimating the association between cruciferous vegetables consumption and risk for breast cancer.

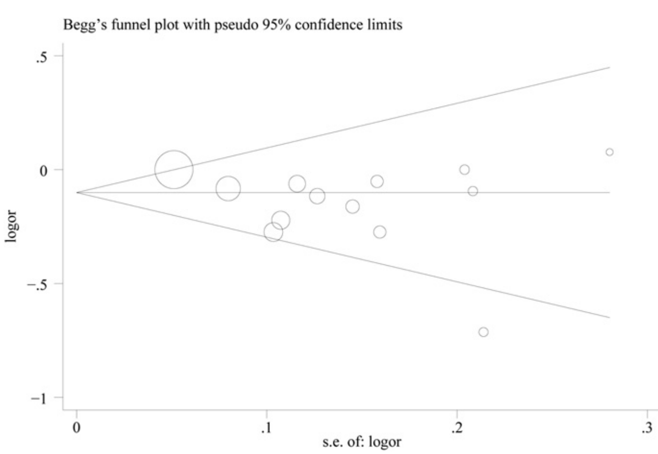

Fig. 3. Funnel plot of cruciferous vegetables consumption and breast cancer risk.

but not premenopausal women. It has been suggested that cruciferous vegetables consumption appear to shift estrogen metabolism in a way consistent with reduced breast cancer risk in postmenopausal women.[30] However, the non-significance might be explained by lack of statistical power owing to a relative small number of studies in premenopausal group.

The protective effect of cruciferous vegetables on breast cancer is biologically plausible. Glucosinolates, the precursors of isothiocyanates (ITCs) and indole-3-carbinol believed to have anticancer properties, are especially rich in cruciferous vegetables.[31] ITCs have been hypothesized to reduce risk of breast cancer through potent inhibition of phase I activating enzymes (e.g., cytochrome P450), and induction of phase II detoxifying enzymes, such as glutathione S-transferases (GSTs).[32,33] These detoxifying enzymes may protect cells against cancer initiation by neutralizing endogenous and exogenous electrophiles in breast tissue. The chemopreventive effect of indole-3-carbinol on breast cancer is likely due in part to their effects on metabolism of estrogen by induction of 2-hydroxylation of estradiol, resulting in nonestrogenic metabolites.[30] Furthermore, indole-3-carbinol can bind to the estrogen receptor (ER), represses ER signaling, downregulates the expression of estrogen-responsive genes,[34] and thus prevents the development of estrogen-enhanced cancers including breast, endometrial and cervical cancers.

Our meta-analysis has several limitations. First, the consumption levels in the lowest and highest categories and the range of consumption varied across studies, and the extent to which confounding factors were controlled also differed among studies, which may bring heterogeneity in the analysis of the highest *versus* the lowest intake categories. Second, most studies were not originally designed to test the cruciferous vegetables/breast cancer hypothesis, and we only assessed total cruciferous vegetables consumption because of the relatively large number of studies on the topic. However, different cruciferous vegetables, such as cabbage, broccoli, and brussels sprouts, may not represent unique exposures because the glucosinolate profile varies across species, thereby attenuating findings for total cruciferous vegetable intake. Third, since we only included published studies in English, possible publication bias is of concern, even though no significant evidence of publication bias was observed.

Table 2
Summary of pooled relative risks of breast cancer in subgroups.

Subgroup	No. of studies	Cases/subjects	Summary OR (95% CI)	Q-test for heterogeneity	
				I^2 score	*p* value
All studies	13[8,9,13,17,18,21,23–29]	18,835/165,236	0.85 (0.77, 0.94)	51.2%	0.047
Menopausal status					
Premenopausal	5[8,9,13,18,21]	9185/145,847	0.88 (0.61, 1.16)	74.0%	0.004
Postmenopausal	7[8,9,13,18,21,23,27]	12,458/152,140	0.83 (0.74, 0.92)	0	0.795
Study design					
Cohort	2[9,13]	3947/135,162	0.86 (0.72, 0.99)	3.0%	0.31
Population-based case-control	8[8,18,21,23,25–28]	9677/20,956	0.86 (0.78, 0.93)	0	0.788
Hospital-based case-control	3[17,24,29]	5211/9118	0.82 (0.45, 1.20)	89.3%	<0.001
Country					
US	8[8,9,13,21,24–27]	9583/146,203	0.86 (0.78, 0.95)	0	0.912
China	3[17,18,28]	3851/8396	0.78 (0.42, 1.14)	83.0%	0.003
Europe	2[23,29]	5401/10,637	0.89 (0.65, 1.12)	84.6%	0.011
Exposure assessment					
Interview	10[8,17,18,21,23,25–29]	12,056/24,592	0.87 (0.75, 0.98)	56.7%	0.014
Questionnaire	3[9,13,23]	6799/140,644	0.82 (0.71, 0.92)	0	0.392

Conclusion

The results of this meta-analysis provide evidence that high cruciferous vegetables consumption may be associated with reduced risk of breast cancer. Given the small number of studies, especially cohort studies, included in this meta-analysis, no firm conclusions can be drawn at the present time. Further prospective cohort studies with larger sample size, well-controlled confounding factors, are needed to affirm the protective effect of cruciferous vegetables on breast cancer.

Conflict of interest statement

None declared.

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