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Review Article

Allium Vegetables Intake and Risk of Breast Cancer: A Meta-Analysis

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Abstract

Background: Intake of allium vegetables may modify the risk of breast cancer. The aim of this study was to examine the association between allium vegetables intake and breast cancer risk via a meta-analysis.

Methods: PubMed, Web of Knowledge, Scopus and Chinese National Knowledge Infrastructure (CNKI) were electronically searched up to June 2021 to identify relevant studies. We used random-effect models to calculate pooled risk estimates and their 95% confidence intervals (CIs) for risk of breast cancer with allium vegetables intake.

Results: A total of 17 studies were included in this meta-analysis on the association of total allium vegetables, garlic and onion intake with breast cancer risk. The combined risk estimate of breast cancer for the highest vs lowest category of total allium vegetables, garlic and onion intake was 0.70 (95% CI: 0.49-0.91, $P < 0.001$), 0.77 (95% CI: 0.61-0.93, $P = 0.016$) and 0.75 (95% CI: 0.53-0.98, $P < 0.001$), respectively. A significant heterogeneity was found among studies for all three pooled analyses.

Conclusion: High intake of allium vegetables may be protective against the development of breast cancer. Further well-designed prospective studies are needed to confirm the results.

Keywords: Allium vegetables; Breast cancer; Garlic; Meta-analysis; Onion

Introduction

Breast cancer is the most common type of cancer and the leading cause of cancer-related deaths in females globally (1). In the past decades, breast cancer mortality was falling in most developed countries, while the incidence has been rising dramatically in several developing countries (2).

Westernization of diet is the one of the possible etiologic reasons for increased incidence in the developing countries, while there has been an ongoing controversy concerning the dietary components that should be reduced and the dietary modification that might contribute to the reduction of breast cancer risk (3). The European Prospective Investigation into Cancer and Nutrition cohort study (EPIC) suggested fruit and vegetable intake was negatively correlated with breast cancer risk (4). Allium vegetables is one of the most consumed vegetables in the world, including garlic, onions, leeks, and chives et al. Findings regarding the association of allium vege-

tables consumption with breast cancer are rare and inconsistent. Some studies have shown that onion and garlic intake was inversely associated with breast cancer, but no such association has been found in other studies (5-12).
The purpose of this study was to identify and synthesize all publications evaluating the relationship between dietary intake of allium vegetables and breast cancer risk using the meta-analytic approach.

Methods

This meta-analysis follows the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (13). We searched the electronic databases PubMed, Web of Science, Scopus and Chinese National Knowledge Infrastructure (CNKI) for the publications up to June 2021 using the following free text words: (allium or garlic or onion or leek or scallion or Chinese chives) and breast cancer. We searched studies published in any language and checked references from these studies to identify other pertinent publications.
Two investigators independently reviewed all identified studies, and included them in this meta-analysis if all the following criteria were met: 1) cohort, nested case-control study, or case-control study design; 2) the exposure of interest was allium vegetables (including garlic, onion, leek, Chinese chives, and others); 3) the outcome of interest was breast cancer; (4) reported risk estimate and its 95% confidence interval (CI). The exclusion criteria were as follows: 1) experimental study; 2) letters or case reports; 3) articles that provided insufficient data or only information for cancer mortality. If there were multiple studies from the same population, we retained the one with the largest number of cases for analysis.
Two investigators extracted all data and resolved any discrepancy by consensus with a third reviewer. Information was recorded as follows: name of the first author and publication year, study design, the country in which the study was conducted, study period, number of case and participants, type of allium vegetables, measure of consumption, study quality, variables of adjustment and exposure assessment. Considering that breast cancer is a relatively rare disease, the relative risk (RR) was assumed approximately the same as OR, and the OR was used as the study outcome.
We assessed the methodological quality of each study using the Newcastle-Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The checklist contains 8 items for the assessment of the patient selection, study comparability, and exposure (for case-control study) or outcome (for cohort study). The range of possible scores is 0–9. We assumed that studies with a score < 7 were of low quality.
We performed separate meta-analyses for: (i) total allium vegetables (the combined consumption of at least two types of allium vegetables), (ii) garlic, and (iii) onion. The OR estimates were pooled for the comparison between the study-specific highest category of intake versus the lowest using the Der Simonian and Laird random effects model. Heterogeneity among studies was assessed with the Q-test and I^2 score (14). Power analysis was also conducted to detect the reliability of the meta-analyses' results according to the formula derived by Tiebel (https://osf.io/w4xrs/). Power analysis was set that the *P* value of the power larger than 80% is acceptable. One study at a time was removed for sensitivity analysis to assess whether the results would be significantly affected by individual studies. The Galbraith plot was also used to detect the possible sources of heterogeneity, and a reanalysis was conducted with exclusion of the studies possibly causing the heterogeneity. Subgroup analyses were conducted by study design, geographic location, and number of included cases. Publication bias was quantitatively assessed using the tests already published (15, 16). All statistical analyses were performed using the STATA 12 software (StataCorp, College Station, TX, USA).

Results

Our literature search yielded 754 publications. Finally, this meta-analysis included 17 publications overall (5-12, 17-25) (Fig. 1). These studies were published between 1993 and 2020, including three prospective studies and 14 case-control studies (comprising a total of 4675 cases). Seven studies were conducted in China, one in Iran, six in Europe, and three in North America. Eight studies evaluated association of breast cancer risk with dietary intake of total allium vegetables intake, 7 studies with garlic intake, and 7 with onion intake. The quality scores of the 17 studies ranged from 5 to 8.

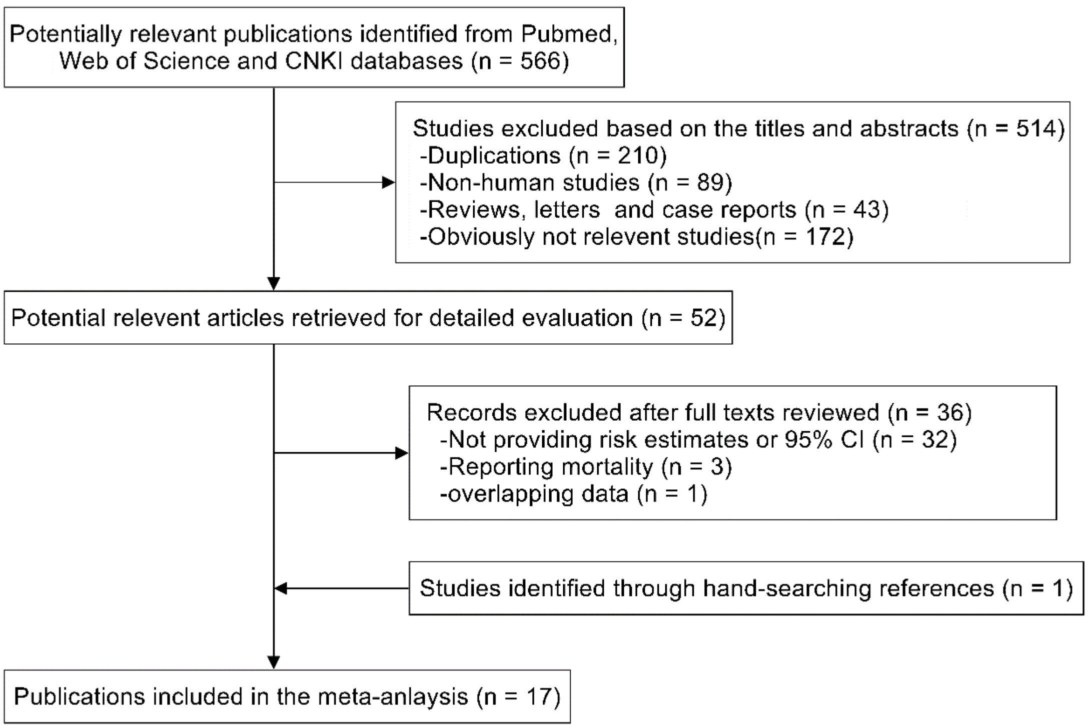

Fig. 1: Flowchart of study selection

Adjusted ORs are available for all studies. Each OR was adjusted for age, nine studies reported an estimate adjusted for parity, nine studies for age at menarche, eight studies for family history of breast cancer, and ten studies for total energy intake. Table 1 presents the characteristics of each study included in our meta-analysis.

Table 1: Characteristics of included epidemiological studies on dietary allium vegetables and risk of breast cancer

Authors and publication year	*Study design*	*Country*	*Study period*	*Case/subjects*	*Type of Allium vegetables*	*Measure of consumption*	*Study quality*	*Variables of adjustment*	*Exposure assessment*
Levi et al. 1993	HCC	Switzerland	1990-1992	107/425	Garlic and onion	Low, medium, high	6	Age, education and total energy intake.	Interview (50 items FFQ)
Dorant et al. 1995	Cohort	Netherlands	1986-1989	469/2182	Garlic supple-	Garlic supplements: Daily	7	Age, parity, age at menarche, age at	Self-administered

					ments, onions, leek	intake Onions: g/day Leek: g/month		first birth, age at menopause, artificially-induced menopause, oral contraceptive use, history of benign breast disease, breast cancer in mother, breast cancer in sister(s), alcohol consumption, Quetelet index, highest level of personal educatiom smoking status, dietary intake of vitamin C and 13-carotene.	questionnaire (150 FFQ)
Chalier et al. 1998	HCC	France	1986-1989	345/690	Garlic and onions	Frequency/week	6	Age, total calories intake, parity, weight, and corporeal surface	Interview (38 items FFQ)
Franceschi et al. 1998	HCC	Italy	1991-1996	2569/5155	Cooked garlic	Low, medium, high	6	Age, center, year of interview, education, physical activity, alcohol, energy intake, and parity.	Interview
Torres-Sánchez et al. 2000	HCC	Mexico	1994-1995	198/396	Onion	Slice/day	6	Age at menarche, total energy intake, number of children and age at 1st birth, lifetime lactation, family history of breast cancer, Quetelet index	Interview (95 items FFQ)
Cao et al. 2001	PCC	China	1992-1996	348/696	Onion	Frequent, infrequent	7	Age, smoking, physical activity, age at menarche, parity and age at first birth, ever had live birth, depression.	Interview
Malin et al. 2003	PCC	China	1996-1998	1459/3015	Allium	Highest vs lowest quintiles	8	Age, education, family history of breast cancer, history of breast fibroadenoma, waist-to-hip ratio, menarche age, physical activity, ever had live birth, age at first live birth, and total energy	Interviews (76 items FFQ)
Lee et al. 2005	HCC	China	1996-1999	250/469	Allium	g/week	7	Age and education	Interview (100 items FFQ)
van Gils et al. 2005	Cohort	Europe	1992-2002	3659/285526	Garlic and onion	Highest vs lowest quintiles	8	Age at menarche, center, energy intake, current oral contraceptive use, current use of hormone therapy,	Self-administered questionnaire (85 items FFQ)

								menopausal status, smoking status, physical activity, and education	
Galeone et al. 2006	PCC	Italy and Swiss	1991-2004	749/2521	Garlic and onion	portions/week	7	Age, study center, education, BMI, energy intake, family history of breast or ovarian cancer, and parity.	Interview (78 items FFQ)
Zhang et al. 2009	PCC	China	2007-2008	435/873	Allium	Highest vs lowest quartiles	7	Age at menarche, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking and total energy intake.	Interview (81 items FFQ)
Chen et al. 2011	PCC	China	2005-2008	106/212	Garlic	Frequent, infrequent, Never	5	Age, residence, mammary mass, depression, irregular menstruation	Interview
Bao et al. 2012	PCC	China	1996-1998	3443/6917	Allium	Highest vs lowest quintiles	7	Total energy, age, education level, ever diagnosed with benign breast disease, first-degree family history of breast cancer, participation in regular exercise, BMI, study phase (I and II), age at menarche, menopausal status, parity, and total meat intake	Interview (76 items FFQ)
Lv et al. 2015	HCC	China	2013	95/380	Garlic	Times/week	7	Age, smoking, age at parity, soy intake, depression.	Interview (146 items FFQ)
Farvid et al. 2016	Cohort	USA	1991-2003	1347/44223	Onion	Servings/week	7	Age, race, history of breast cancer in mother or sisters, history of benign breast disease, smoking, height, physical activity, BMI at age 18, weight change since age 18, age at menarche, parity and age at first birth, oral contraceptive use, menopausal status, menopausal hormone use, age at menopause, and intakes of alcohol and energy	Self-administered questionnaire (130 items FFQ)

Pourzand et al. 2016	HCC	Iran	2012-2013	285/582	Garlic and onion	g/day	6	Age, menopause, total calorie, dietary fat, dietary fiber, and body mass index	Interview (136 items FFQ)
Desai et al. 2020	PCC	Puerto Rican	2008-2014	314/660	Allium	Low, medium, high	7	Age, education, parity, family history of breast cancer, BMI, age at menarche, smoking, total energy	Interview

Abbreviation: HCC, hospital-based case-control study; PCC, population-based case-control study; BMI, body mass index

Total allium vegetables intake

The multivariable-adjusted ORs for each study and all studies combined for the highest vs lowest categories of total allium vegetables intake are shown in Fig. 2. Results from studies on total allium vegetables intake in relation to breast cancer risk were inconsistent, with significant heterogeneity (I^2 = 84.8%, $P < 0.001$). The pooled OR of breast cancer for the highest vs lowest categories of total allium vegetables intake was 0.70 (95% CI, 0.49-0.91). With data provided by the 8 studies, the statistical power of 1.0 could be achieved. There was significant publication bias detected with Egger's ($P = 0.029$) and Begg's ($P = 0.019$, Fig. S1A) test (Supplementary figures are not published here. Interested readers may contact the corresponding author to reach the materials).

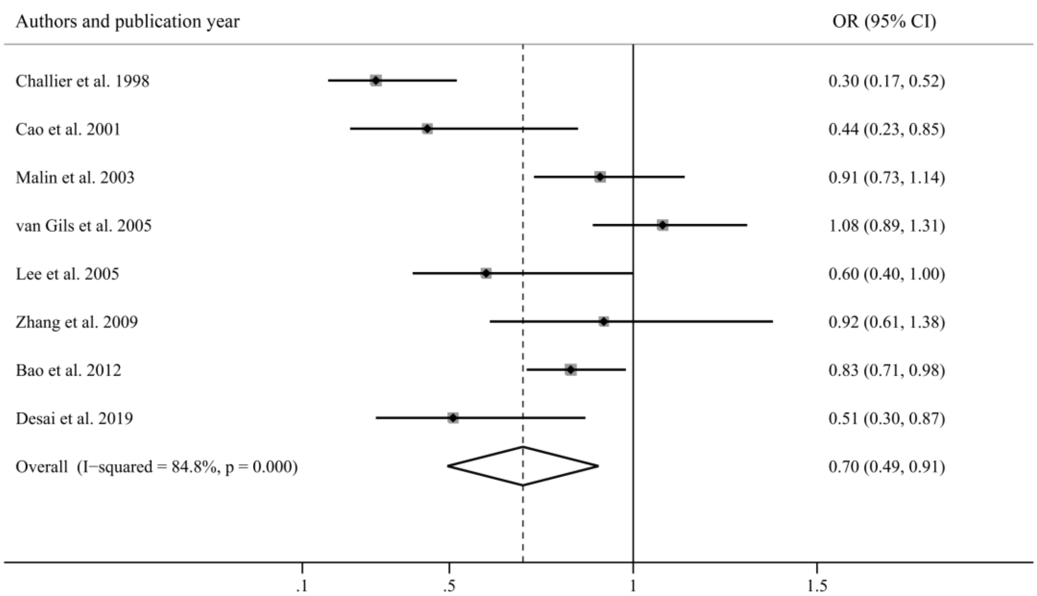

Fig. 2: A forest plot of the pooled OR for allium vegetables intake and breast cancer risk

We next performed sensitivity analysis to explore the source of the heterogeneity among studies of allium vegetables intake and breast cancer. The sensitivity analysis removing one study at a time and calculating the pooled ORs for the rest studies showed that no single study substantially influenced the pooled OR. Through the Galbraith plot, we noted that 2 studies (6, 20) were the major sources of heterogeneity (Fig. S2A), which reported the most positive and negative relationships, respectively. The summary OR varied little after excluding the 2 studies (OR = 0.72; 95% CI, 0.56-0.88) with no heterogeneity among studies.

In the subgroup analyses, we pooled the OR by study design (cohort or case-control), geographical region (US, Europe and Asia), and number of included cases (≥ 300 or < 300). A statistically significant protective effect of allium vegetables intake on breast cancer was observed in case-control studies (OR = 0.64; 95% CI, 0.44-0.85), while no such effect in cohort studies (OR = 1.08; 95% CI, 0.89–1.31). Also, the inverse associations were found in US (OR = 0.51; 95% CI, 0.30-0.87), Asia (OR = 0.76; 95% CI, 0.60-0.92), but not in Europe (OR = 0.99; 95% CI, 0.59-1.38). When stratifying by number of cases, the OR estimates showed allium vegetables intake was consistently associated with reduced risk of breast cancer (Table 2).

Table 2: Subgroup analyses between the intake of allium vegetables, garlic, onion and the risk of breast cancer

	Allium vegetables				***Garlic***				***Onion***			
	N	OR (95%CI)	I^2(%)	*P*-Value	N	OR (95%CI)	I^2(%)	*P*-Value	N	OR (95%CI)	I^2(%)	*P*-Value
Study design												
Cohort	1	1.08 (0.89-1.31)	-	-	1	0.75 (0.14-1.38)	-	-	1	0.95 (0.61-1.47)	-	-
Case-control	6	0.64 (0.44-0.85)	81.8	< 0.001	6	0.77 (0.60-0.94)	67.7	0.009	6	0.73 (0.49-1.12)	94.2	< 0.001
Geographical region												
USA	1	0.51 (0.30-0.87)	-	-	-	-	-	-	2	0.53 (0.15-1.87)	95.4	< 0.001
Asia	5	0.76 (0.60-0.92)	53.1	0.074	3	0.65 (0.20-1.10)	72.0	0.028	1	0.85 (0.53-1.36)	-	-
Europe	2	0.99 (0.59-1.38)	36.1	0.209	4	0.89 (0.81-0.97)	0	0.72	4	0.83 (0.63-1.09)	60.0	0.058
Samples												
≥ 300	6	0.71 (0.48-0.94)	86.8	< 0.001	3	0.90 (0.82-0.98)	0	0.895	4	0.98 (0.94-1.02)	0	0.515
< 300	1	0.60 (0.40-1.00)	-	-	4	0.65 (0.34-0.96)	60.4	0.056	3	0.49 (0.18-0.80)	73.2	0.024

Garlic intake

Seven studies reported results on garlic intake with breast cancer risk (7, 8, 10, 17, 21-23). The multivariable adjusted ORs of breast cancer for each study and all studies combined for the highest versus the lowest category of garlic intake are shown in Fig. 3. The summary ORs were 0.77 (95% CI, 0.61-0.93) for garlic intake in a random-effects model, with significant heterogeneity (I = 61.5%, *P* = 0.016). The statistical power was 1.0. No publication bias was detected either with Begg's (*P* = 0.23, Fig. S1B) or Egger's test (*P* = 0.219). The sensitivity analysis removing one study at a time and calculating the pooled ORs for the rest studies showed that no single study substantially influenced the pooled OR. Through the Galbraith plot, we noted that no studies were identified as the major sources of heterogeneity (Fig. S2B).

In the subgroup analyses, the protective effect of garlic intake on breast cancer risk appeared limited to the case-control studies (OR = 0.77, 95% CI = 0.60-0.94) and the European populations (OR = 0.89, 95% CI, 0.81-0.97). When stratified by number of cases, the significant protective effects of garlic intake on breast cancer were observed in both subgroups.

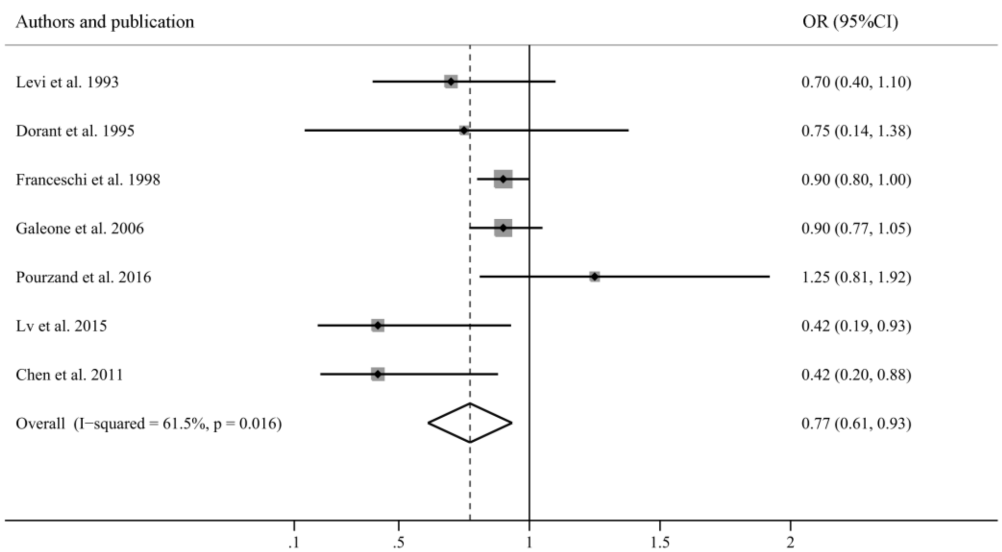

Fig. 3: A forest plot of the pooled OR for garlic intake and breast cancer risk

Onion intake

Figure 4 shows the results of onion intake and breast cancer risk. Seven studies reported results onion intake (7, 8, 10, 11, 17, 21, 24), and the summary OR was 0.75 (95% CI: 0.53-0.98) in a random-effects model, with evidence of strong heterogeneity ($P < 0.001$, $I^2 = 93.1\%$).

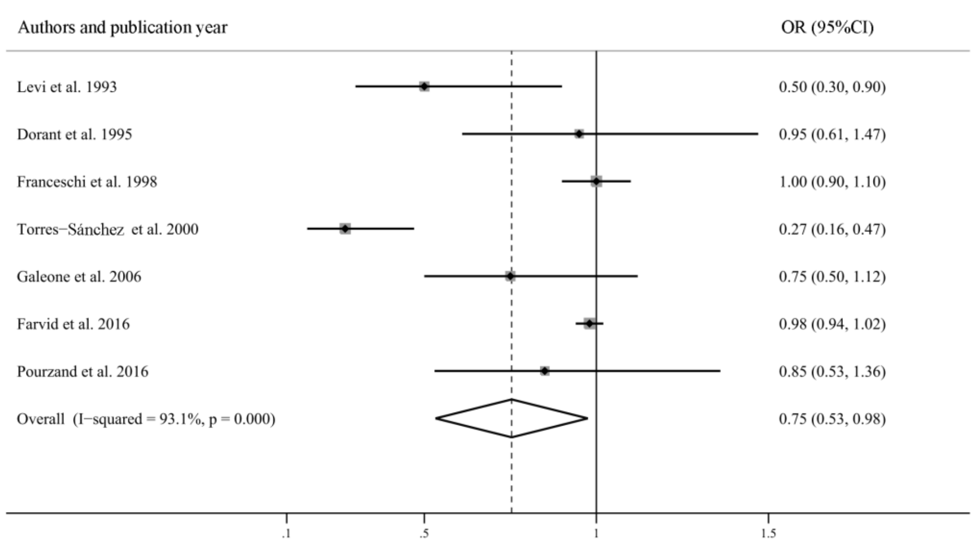

Fig. 4: A forest plot of the pooled OR for onion intake and breast cancer risk

Enough statistical power was reached (P_{power} = 1.0). The sensitivity analysis indicated that the no single study substantially influenced the pooled OR. Also, the Galbraith plot showed that 2 studies (11, 17) were the major sources of heterogeneity (Fig. S2C). The summary OR was 0.98 (95% CI, 0.94-1.01), and no significant heterogeneity existed (P = 0.617, I^2 = 0%) after excluding the 2 studies. A borderline publication bias was detected with Begg's (P = 0.035, Fig. S1C) but not with Egger's test (P = 0.077). The subgroup analyses consistently showed that onion intake was not associated with incidence of breast cancer except for studies including cases less than 300 (OR = 0.49; 95% CI, 0.18-0.80) (Table 2).

Discussion

Several meta-analyses have assessed the association between allium vegetables, garlic, and onion intake and risk of other cancers (26-28). High intake of allium vegetables intake may reduce the risk of gastric cancer (27). Zhou et al. (28) found a significantly decreased risk of prostate cancer for intake of allium vegetables and garlic but not onions. Another meta-analysis of observational studies found an inverse association between allium vegetables intake and the risk of squamous cell carcinoma of the upper aerodigestive tract, but this relation was unclear for esophageal adenocarcinoma (26). However, findings from epidemiological studies were inconsistent concerning the associations of allium vegetables and the risk of breast cancer. The present meta-analysis indicated that increased allium vegetables, garlic, and onion intake might be significantly associated with a lower risk of breast cancer.

There was significant heterogeneity among all three pooled analyses, which could distort the associations. The heterogeneity might be caused by differences in the definition of the highest category of consumption, exposure range, and dietary assessment methods (interview vs self-administered questionnaire) in each study. When we removed the studies that obviously contributed to the heterogeneity through the Galbraith plot and then repeated the meta-analysis, the significant inverse relationship persisted for analysis of allium vegetables, but did not exist for onion without any significant heterogeneity. These results indicated our findings were less robust and more likely affected by the heterogeneity for onion intake analysis. In the subgroup analysis, we found a significant risk reduction from case-control studies, but no association from cohort studies for each analysis (totally three cohort studies were included), indicating that our conclusion was dependent on case-control studies. In general, cohort studies provide stronger evidence regarding an association than case-control studies which are more prone to recall and selection bias. Therefore, further well-designed cohort studies are warranted.

Our results are in line with the inhibitory role of allium-derived compounds on breast carcinogenesis. Allium vegetables are rich in a variety of bioactive substances, such as organosulfur compounds and flavonoids, which have shown beneficial effects against various cancers (29). Diallyl trisulfide, a natural organosulfur compound from garlic, exhibits effective antitumor properties (30). Preclinical studies have reported protective effects of diallyl trisulfide against breast cancer in "in vivo" and "in vitro" models via numerous mechanisms, including inhibition of cell proliferation, alteration of enzyme activities, and immune modulation (31-33). S-allylcysteine, a compound found in onions, has been suggested to suppress cell proliferation, adhesion and invasion in cultured human breast-cancer cells (34). Quercetin, also a constituent of onions, modulates several signal pathways to reduce the progression of breast cancer cells (35). Allicin, a component of garlic, has the ability to inhibit proliferation of the MCF-7 human breast cancer cell lines (36). Both onion and garlic have free radical scavenging activities, which is another proposed anticancer mechanism (37).

The strengths and limitations should be acknowledged before generalizing the results of this meta-analysis. To begin with, this is the first meta-analysis to assess the relationship between allium vegetables intake and risk of breast cancer. Another strength is that most of the included studies applied an interview-administered questionnaire. It is believed that self-reported questionnaires for food assessment might lead to some misclassification of participants in terms of exposure. Furthermore, the pooled sample size for this meta-analysis was large enough to obtain sufficient statistical power. In the meanwhile, the present study also has several limitations. First, the meta-analysis cannot solve the problem of confounding factors inherent in the study. Although individual studies in this meta-analysis have considered at least 3 potential confounding factors, only half of the studies included in the meta-analysis controlled for parity and age at menarche, which may bias the results. No separate analyses in strata of adjustment for parity and age at menarche were possible given the limited number of studies stratifying on such covariates. Second, we were unable to perform a dose-response analysis because the original data form included studies used different units to report allium vegetables intake (grams, portions or servings), or it was reported as frequency of consumption with no information on the portion size. Third, regarding publication bias, although no such bias was detected for the meta-analyses on garlic, both the analysis of allium vegetables and onion intake showed a publication bias of significance. However, given the small number of studies in the stratified analysis, the validity of publication bias testing should be interpreted with caution. Fourth, there are significant differences in the bioavailability and activity of bioactive compounds if allium vegetables are consumed raw or cooked, and by different modalities of cooking (38). For example, a study reported that the allicin concentration was higher in fresh than in heated raw garlic extracts, resulting in a greater anti-inflammatory effect and the flavonoid content in onions is significantly reduced by frying, sautéing, boiling, steaming, microwaving, and dehydrating (39). However, most studies did not provide information in terms of cooking methods except for one (8).

Due to the limitations mentioned above, better designed prospective research with strict control of confounders should be conducted to confirm our findings in the future. In addition, these future studies should focus on assessing the dose-response analysis, clarifying potential biological mechanisms, providing hypotheses on the lag time necessary for the causal relationship, and then instruct clinicians about breast cancer prophylaxis.

Conclusion

High allium vegetables intake, including garlic and onion, were associated with lower risk of breast cancer. Caution is needed in interpreting the association, which might be due to measurement errors, uncontrolled confounders, or publication bias.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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