Association and mechanism of garlic consumption with gastrointestinal cancer risk: A systematic review and meta-analysis

YANGYANG WANG1-3, PING HUANG2, YUFEI WU1-3, DUANRUI LIU1,3, MINGYU JI2, HUANJIE LI1,2 and YUNSHAN WANG1,3

1School of Medicine, Cheelpoo College of Medicine, Shandong University, Jinan, Shandong 250012; 2Medical Research and Laboratory Diagnostic Center; 3Basic Medical Research Center, Jinan Central Hospital Affiliated to Shandong First Medical University, Jinan, Shandong 250013, P.R. China

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Abstract. Gastrointestinal cancer is one of the most commonly diagnosed cancer type worldwide, with millions of cases per year. The aim of this review was to investigate the relationship between garlic intake and the risk reduction of gastrointestinal cancer. We performed saturated data mining on various public domain databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/landing?status=grey), and Cochrane Library (https://www.cochranelibrary.com/), with key terms including: ‘garlic’, ‘allium’, ‘stomach’, ‘gastric’, ‘colon’, ‘neoplasms’, ‘cancer’ and ‘tumor’. Furthermore, we identified additional references through expert manual curation. Finally, a meta-analysis was conducted to determine whether garlic intake reduces the risk of gastric and/or colorectal cancer. The association between garlic intake and reduction in the risk of gastric cancer [odds ratio (OR)=0.65, 95% confidence interval (CI)=0.49-0.87, P<0.001] were clear. Nine studies on garlic intake and colorectal cancer showed that garlic reduced cancer risk with a statistical significance (OR=0.75, 95% CI=0.65-0.87, P<0.001). We summarized that four main organic sulfides in garlic, diallyl disulfide (DADS), diallyl trisulfide (DATS), S-allylmercaptocysteine (SAMC) and allicin, may contribute to the regulation of tumor cell apoptosis, migration and the cell cycle. We identified the association between garlic intake and reduced risk of gastric and colorectal cancers and hypothesized that the active ingredients in garlic may act on multiple pathways to reduce the risk of gastrointestinal tumors according to published papers. Importantly, the potential tumor-preventing effect of these garlic ingredients warrants further investigation in regards to the specific mechanism of the underlying antitumor activities.

Introduction

Gastrointestinal cancer is a health issue with worldwide concern, of which gastric and colorectal cancers are the most common types (1,2). Despite the declining incidence and mortality, gastric cancer remains the third leading cause of cancer-related mortality in the world (1,3). Nearly one million gastric cancer cases are diagnosed worldwide yearly, about half of which are found in the Chinese population (3). The incidence of colorectal cancer ranks third in the world, with highest morbidity and mortality in Asian populations (4). This distribution may be related to particular diet habits, increased level of stress and/or the Helicobacter pylori (H. pylori) infection prevalence in the Asian population (5,6). China and South Korea prefer high-salt foods such as pickles and kimchi. Koreans consume more than twice the daily salt intake recommended by the World Health Organization (7,8), and a high-salt diet can lead to a series of gastrointestinal diseases. Approximately half of the world's population is infected with H. pylori, while more than 55% are found in China (9,10). Some studies have shown the relationship among vegetable consumption, gastrointestinal tumors and H. pylori (11-14), confirming that the increased consumption of fibers that are abundant in fresh fruits and vegetables is correlated with a reduced risk of gastrointestinal cancer (11). Historically, garlic consumption has been associated with medicinal properties in ancient cultures of Indochina, the Mediterranean and Northern Africa (15). Garlic was shown to be able to reduce the risk of carcinogenesis in breast cancer, pancreatic cancer and esophageal cancer models (16-18). The S-allyl cysteine, diallyl disulfide, and other compounds found in garlic were suggested to have anticancer effects in cellular models (15,19,20). Many potential anticancer mechanisms of these compounds were proposed, including the inhibition of cell proliferation, changes in enzyme activity and immune regulation (21,22). The active ingredients in garlic oil correspond mainly to a family of organosulfur molecules, which selectively increase redox stress in cancer cells, leading to apoptosis and death (23).
Previous meta-analyses and reviews exploring the relationship between garlic consumption and the risk of gastric and colorectal cancers have come to inconsistent conclusion (4,14,24-30). While some studies have found that garlic intake could reduce the risk of gastric and colorectal cancers (14,30), others have shown that this effect may be overestimated (28). In a recent study by Li et al (13) with a follow-up of 22.3 years, garlic supplementation was found to be associated with reduced gastric cancer mortality (OR=0.81, 95% CI=0.57-1.13), with a delayed effect on gastric cancer mortality. Although this finding provides a potential opportunity for the prevention of gastric cancer, further large-scale intervention trials are needed to confirm the effect. Based on the prospective data from the Nurses' Health Study involving 121,700 nurses [relative risk (RR)=1.21, 95% CI=0.94-1.57] and the Health Professionals Follow-up Study (RR=1.00, 95% CI=0.71-1.42) involving 512,529 male health professionals, Meng et al (31) found no association between garlic consumption and the risk of colorectal cancer. However, this study was excluded in this research due to the lack of OR or RR data. Different diets in various populations, various levels of garlic consumption, and diverse patterns of garlic intake may cause inconsistent results from the different studies. Therefore, the effect of garlic on gastrointestinal cancer needs to be further confirmed. We conducted this meta-analysis to update the epidemiological evidence for the association between garlic and gastrointestinal cancer.

Materials and methods

Search strategy. This systemic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study was registered in PROSPERO (CRD42020179464). The authors completed the data search in September 2021. All relevant studies that related to garlic intake for gastric and colorectal cancers from 1980 to 2021 were identified by searching in the following databases: Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/landing?status=grey) and Cochrane Library (https://www.cochranelibrary.com/), with key terms including: ‘garlic’, ‘allium’, ‘stomach’, ‘gastric’, ‘colon’, ‘neoplasms’, ‘cancer’ and ‘tumor’. The detailed searching strategies in each database are shown in Tables SI-SIII. All studies that met the inclusion criteria included: i) reviews or meta-analyses; ii) non-English literature; iii) studies that lacked OR or RR data, or without sufficient data estimation results; iv) studies for which animal, cell, in vitro, and in vivo experiments were excluded. Since the majority of related studies were published in English, we chose not to include non-English studies which were very few and had lack of representativeness. The studies that were included were all non-truncated ones.

Data extraction. Data mining was performed by two investigators. Disagreements were resolved by consultation with a third investigator. The following information was extracted: author, year of publication, study period, study type, country, number of subjects, risk estimates and their 95% CI, description of garlic intake categories, and adjusted variables.

Risk of bias assessment. For randomized controlled trials (RCTs), we assessed the risk of bias using the Cochrane Risk of Bias assessment tool (32). The following characteristics were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. According to the recommendations of the Cochrane Handbook, a judgment to risk of bias was determined as three categories, including low risk, unclear risk and high risk. We used the Newcastle-Ottawa Scale (NOS) to assess the risk of bias in nonrandomized studies and scored the studies in three categories: selection (four questions), comparability of study groups (two questions), and ascertainment of exposure or outcome (three questions). Regarding the comparability, the study groups were awarded a maximum of two points; all the other questions were assigned a score of one point (33).

Statistical analysis. We first collected the OR of gastric cancer in various studies. Since the incidences of gastric cancer and colorectal cancer are relatively low, the approximate OR was obtained based on the RR. Then we explored the sources of heterogeneity and conducted a subgroup analysis by garlic intake level, geographic area, and the type of study.

The heterogeneity was assessed using the Cochrane's Q test and I² statistic. P-values <0.1 and I² values >50% suggested the existence of heterogeneity. If significant heterogeneity existed, a random effect model was selected; otherwise, the fixed-effects model was used. Meanwhile, I² values of <30%, 30-60%, and >60% were considered to indicate low, moderate, and high heterogeneity, respectively. Results were assessed using forest plots. All data analysis was performed by STATA 12.0 (https://www.stata.com/).

Sensitivity analysis and subgroup analysis. Sensitivity analysis was performed to identify potential sources of heterogeneity according to garlic consumption level, research type and geographical area. Subgroup analysis was conducted to identify the cause of heterogeneity. Random effect model and fixed effect model were selected according to different degrees of heterogeneity.

Publication bias. Publication bias was assessed by conducting Begg's and Egger's funnel plot asymmetry tests, a P-value <0.1 suggested publication bias with statistical significance.
Results

Study selection and characteristics. A total of 648 articles were initially identified, of which 226 articles were excluded as duplicate studies. Then we reviewed the titles and abstracts of each literature according to inclusion and exclusion criteria. We excluded additional articles, among which 323 were irrelevant to this study, 54 were meta-analyses and reviews, and 14 were non-English literature. After a careful review of the full texts in the remaining 31 articles, we finally included 20 articles after excluding 4 articles from the same study and 7 articles with insufficient data. OR, odds ratio; RR, relative risk.

Overall and subgroup analysis of evidence. We conducted an overall estimation by categories of garlic consumption (Fig. 2). The ORs of all the studies were extracted for the
| Authors of the study (year) | Country       | Study design            | Study period | Cases/Controls          | Garlic consumption types                      | Consumption | OR/RR (95% CI) | Adjustment                                                                                     | (Ref(s.) |
|-----------------------------|---------------|-------------------------|--------------|-------------------------|-----------------------------------------------|-------------|---------------|---------------------------------------------------------------------------------------------|-------|
| You et al (1989)            | China         | Population-based case-control study | 1984-1986   | 564/1,131               | Garlic                                        | 0 (kg/year) | 1.00          | Age, sex, family income, and intake of other allium vegetables                               | (38)  |
| Dorant et al (1996)         | The Netherlands | Cohort study            | 1986-1990   | 152 (male 119, female 33) | Garlic supplement                              | No supplements | 1.00          | Age, alcohol intake, vitamin C intake, and β-carotene as continuous variables and sex, smoking status, education, history of stomach disorders, and family history of stomach cancer as categorical variables | (36)  |
| Gao et al (1999)            | China         | Population-based case-control study | 1995-1997   | 153 (male 140, female 53) | Garlic                                        | <1 time/month | 1.00          | Age, sex, income, smoking, drinking, tea consumption and intake of leftovers, pickled vegetables, meat, fruit, tomatoes, eggs and snap beans | (40)  |
| Muñoz et al (2001)          | Venezuela     | Population-based case-control study | 1991-1997   | 292/485                  | Garlic                                        | Less than once/week | 1.00          | Age, sex and SES                                                                            | (37)  |
| Takezaki et al (2001)       | China         | Population-based case-control study | 1996-2000   | 187 (male 137, female 50) | Garlic                                        | <1 time/week | 1.00          | Age, sex, smoking and drinking habits                                                      | (18)  |
| De Stefani et al (2001)     | Uruguay       | Hospital-based case-control study   | 1997-2000   | 160 (male 114, female 46) | Garlic                                        | Everyday     | 0.67          | Age, sex, residence, urban/rural status, education, body mass index (BMI), and total energy intake, and total fruit intake | (34)  |
| Setiawan et al (2005a)      | China         | Population-based case-control study | 1991-1993   | 750 (male 478, female 272) | Garlic                                        | Never        | 1.00          | Matching variables (age, sex, educational, BMI, pack-years of smoking, alcohol drinking, salt intake, and vegetable and fruit intake) | (35)  |
| Authors of the study (year) | Country | Study design | Study period | Cases/Controls | Garlic consumption types | OR/RR (95% CI) | Adjustment | (Refs.) |
|-----------------------------|---------|--------------|--------------|---------------|-------------------------|----------------|------------|--------|
| Setiawan et al (2005b)      | China   | Population-based case-control study | 1991-1993 | 201 (male 143, female 58)/201 (male 143, female 58) | Garlic | Never | 1.00 | Matching variables (age, sex), education, BMI, pack-years of smoking, alcohol drinking, salt intake, and vegetable and fruit intake | (35) |
| Pourfarzi et al (2009)      | Iran    | Population-based case-control study | 1999-2005 | 217 (male 151, female 66)/394 (male 265, female 129) | Garlic | Never or infrequently | 1.00 | Sex, age group, education, family history of GC, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and H. pylori. | (41) |
| Kim et al (2018) NHS        | USA     | Cohort study | 1984-2014 | 138/76,948 | Garlic | Never | 1.00 | Age, Caucasian, BMI, physical activity, smoking status, alcohol consumption, current multivitamin use, current aspirin use, personal history of diabetes mellitus, and intakes of total calorie, red/processed meat, fruits, vegetables, and coffee | (39) |
| Kim et al (2018) HPFS       | USA     | Cohort study | 1984-2014 | 154/46,244 | Garlic | Never | 1.00 | Age, Caucasian, BMI, physical activity, smoking status, alcohol consumption, current multivitamin use, current aspirin use, personal history of diabetes mellitus, and intakes of total calorie, red/processed meat, fruits, vegetables, and coffee | (39) |
| Li et al (2019)             | China   | Randomized controlled trial | 1995-2017 | 151/3,241 | Garlic supplementation | Twice a day | 0.81 (0.57-1.13) | Baseline histology, age, sex, history of ever using alcohol, and history of ever smoking | (13) |
| Authors of the study (year) | Country | Study design          | Study period       | Cases/Controls | Garlic consumption types | OR/RR (95% CI) | Adjustment                                                                                           | (Refs.) |
|----------------------------|---------|-----------------------|--------------------|----------------|--------------------------|----------------|-------------------------------------------------------------------------------------------------------|---------|
| **Yuan et al (2020)**      | China   | Hospital-based case-control study | 2014-2016          | 180/180        | Garlic                   | 0.35 (0.18-0.67) | Dietary/lifestyle habits, psychological factors, serum PG I level, serum PG II level, PG I/II ratio, serum G-17 level and H. pylori infection | (47)    |
| **Steinmetz et al (1994)** | USA     | Prospective cohort Study | 1986-1990          | 212/35004      | Garlic                   | L1 (0)          | Age and energy intake                                                                                   | (45)    |
| **Witte et al (1996)**     | USA     | Case control study     | 1991-1993          | 488 (male 325, female 163)/488 | Garlic | None | 1.00 | Race, BMI, physical activity, smoking, calories, and saturated fat using conditional logistic regression, dietary fiber, folate, β-carotene, and vitamin C | (49)    |
| **Dorant et al (1996) (colon)** | The Netherlands | Cohort study | 1986-1989 | 293 (male 150, female 143)/3,123 | Garlic | No supplement | Exclusively garlic | Age, vitamin C and J-carotene as continuous variables, and sex, smoking status, education, family history of intestinal cancer, previous history of chronic intestinal disease or cholecystectomy as categorical variables | (42)    |
| **Dorant et al (1996) (rectum)** | The Netherlands | Cohort study | 1986-1989 | 150 (male 93, female 57)/3,123 | Garlic | No supplement | Exclusively garlic | Age, vitamin C and J-carotene as continuous variables, and sex, smoking status, education, family history of intestinal cancer, previous history of chronic intestinal disease or cholecystectomy as categorical variables | (42)    |
| **Franceschi et al (1997) (colon)** | Italy | Case control study     | 1991-1996          | 1,225/5,155    | Cooked garlic            | 0.9 (0.8-1.0)   | Age, sex, center, year of interview, education, physical activity, alcohol and energy intake | (46)    |
Table I. Continued.

| Authors of the study (year) | Country | Study design | Study period | Cases/Controls | Garlic consumption types | Consumption | OR/RR (95% CI) | Adjustment | (Refs.) |
|-----------------------------|---------|--------------|--------------|----------------|--------------------------|-------------|----------------|------------|--------|
| Franceschi et al (1997) (rectum) | Italy | Case control study | 1991-1996 | 728/5,155 | Cooked garlic | 0.9 (0.8-1.0) | Age, sex, center, year of interview, education, physical activity, alcohol and energy intake | (46) |
| Levi et al (1999) | Switzerland | Case control study | 1992-1997 | 223 (male 142, female 81)/491 (male 211, female 280) | Garlic | Low 0.51 (0.35-0.74), Medium 0.32 (0.18-0.57) | Age, sex, education, smoking, alcohol, BMI, physical activity and total energy intake | (44) |
| Galeone et al (2006) | Italy | Case control study | 1991-2004 | 2,280 (male 1,318, female 962)/4,765 (male 2,403, female 2,362) | Garlic | None or low 0.88 (0.78, 0.98), Intermediate 0.74 (0.63-0.86) | Age, sex, study center, education, BMI, energy intake, alcohol consumption, smoking habit, and physical activity | (48) |
| Annema et al (2011) | Australia | Population-based case-control study | 2005-2007 | 834 (male 514, female 320)/939 (male 551, female 388) | Garlic | <0.02 (servings/day) 0.92 (0.67-1.26), 0.02-<0.14 (servings/day) 0.84 (0.62-1.15), 0.14-<0.28 (servings/day) 0.86 (0.68-1.09), 0.28+ (servings/day) 1 | Adjusted for sex, age, BMI at age 20 years, energy intake, multivitamin use, alcohol consumption, physical activity, smoking, diabetes and socioeconomic status | (50) |
| Wang et al (2018) | China | Case control study | 2015-2016 | 317 (male 145, female 172)/317 (male 146, female 171) | Garlic | 0.499 (0.341-0.732) | | (43) |
| Wu et al (2019) | China | Hospital-based matched case-control study | 2009-2011 | 833/833 | Garlic | <0.60 (kg/year) 1, 0.60-2.60 (kg/year) 0.49 (0.35-0.66), 2.60-3.65 (kg/year) 0.43 (0.30-0.59), >3.65 (kg/year) 0.56 (0.39-0.79) | BMI, family history of CRC (first degree), education level, smoking, passive smoking, alcohol, the consumption of red meat, milk, other vegetables, fruit, total energy, fiber, calcium, fat, vitamin C, vitamin D, cholesterol, and folic acid | (12) |
Figure 2. Associations between garlic intake and gastrointestinal cancer risk by garlic consumption. The (number/number) after each study in the figure indicates the (Cases/Controls). Vertical solid black line: invalid line; red dashed line: pooled effect size; horizontal black solid line: the width of the line represents the confidence interval (CI) of each study, the black diamond in the middle represents the OR of each study, and the gray square represents the weight of each study. Others: We have included some studies that differed from other classifications of garlic intake into this category. **(A)** Forest plots for the associations between garlic intake and gastric cancer risk by garlic consumption. The OR obtained by the pooled analysis was 0.65 (95% CI=0.49‑0.87). **(B)** Forest plots for the associations between garlic intake and colorectal cancer risk by garlic consumption. The meta-analysis using the random-effects model showed a combined estimated OR of 0.75 (95% CI=0.65‑0.87), suggesting that garlic intake could reduce the risk of colorectal cancer. OR, odds ratio; ES, effect size.
The OR obtained by the pooled analysis was 0.65 (95% CI=0.49-0.87, P<0.001), indicating that garlic intake was associated with a lower risk of gastric cancer in individuals compared with those without garlic intake (Fig. 2A). Participants who consumed garlic every day had a significant lower risk of gastric cancer than those who did not consume garlic.

In the subgroup analysis by geographic area (Fig. S1), the estimated OR of the studies in Asia, Europe and America was 0.53 (95% CI=0.38-0.73), 1.27 (95% CI=0.61-2.64), 0.87 (95% CI=0.52-1.47, P<0.05), respectively (Table SIV). In addition, the comprehensive analysis of prospective studies showed that garlic intake correlated with a small reduction in gastric cancer (OR=1.07, 95% CI=0.79-1.47), while the retrospective studies showed garlic intake had a more significant effect (OR=0.50, 95% CI=0.39-0.64) (Fig. S2).

We found that among those 11 included studies, 2 studies (36,39) containing 126,976 subjects showed that garlic intake had no significant association with the incidence of gastric cancer (OR=1.36, 95% CI=0.93-1.99), including 12,6976 subjects, and 9 studies showed that garlic intake could significantly reduce the incidence of gastric cancer (OR=0.54, 95% CI=0.41-0.70) (P<0.05) (Fig. 3).

A total of 9 studies estimated the association between garlic intake and the risk of colorectal cancer (Fig. 2B). The meta-analysis using the random-effects model showed a combined estimated OR of 0.75 (95% CI=0.65-0.87, P<0.001), suggesting that garlic intake could significantly reduce the risk of colorectal cancer. Among the 9 included research studies, only Dorant et al (42) and Franceschini et al (46) estimated the OR values for colon cancer and rectal cancer separately, without providing the total OR value.

Compared to the retrospective studies (OR=0.72, 95% CI=0.62-0.84, P<0.001), the results of the prospective study (OR=1.01, 95% CI=0.62-1.65, P<0.01) showed an insignificant effect of garlic intake on reducing the risk of colorectal cancer (Table SV; Fig. S3). Subgroup analyses of geographical regions (Fig. S4) showed that garlic intake significantly reduced the risk of colorectal cancer in Asia compared to other regions.

### Heterogeneity assessment and sensitivity analysis

The random effect model suggested a strong heterogeneity with I²=69.8%, and P<0.1 in the studies of garlic and gastric cancer which were selected for the meta-analysis. Therefore, we conducted Galbraith test to further identify the source of heterogeneity. The result of Galbraith test showed that the studies of Gao et al (40) and Kim et al (39) were the main source of heterogeneity.
sources of heterogeneity (Fig. 4A). The result of sensitivity analysis showed that our results were stable, and there was no significant difference in the pooled results (Fig. 5A).

For the 9 studies of garlic and colorectal cancer, a significant heterogeneity was also suggested ($I^2=71.4\%$, $P<0.001$). According to the results of Galbraith test, three studies (Wu et al, Levi et al, and Wang et al) were the main sources of heterogeneity.
Our meta-analysis suggested that garlic can reduce the risk of gastrointestinal cancers, and most of the included studies are retrospective case-control studies, lacking blinding and randomized control (53), we still found that garlic intake was associated with a reduced risk of gastric and colorectal cancer compared with the non-intake of garlic. Although a previous meta-analysis by others showed that the protective effect of garlic on gastric and colorectal cancer may be overestimated (28), the results of the comprehensive analysis in this study indicated the preventive function of garlic in gastrointestinal tumors.

A further review was conducted on the molecular mechanisms of the anticancer effects of garlic (Fig. 8). Based on previous literature, garlic contains a variety of organic sulfur compounds, mainly including S-allylmercaptocysteine (SAMC), diallyl disulfide (DADS), diallyl trisulfide (DATS) and allicin, which are the main components which produce potential antitumor effects. We searched the Pubmed database with key terms including 'gastrointestinal tumors', 'garlic', 'mechanism', 'pathways', and reviewed biological functions of these four organic sulfur compounds. These organic sulfur compounds demonstrate potential antitumor activity through various underlying mechanisms. First, organic sulfur compounds can regulate the cell cycle. DADS and DATS can activate the P53/P21 pathway, while DADS can inhibit the expression of cyclin B1, cdc2, and cdc25c proteins, leading to G2/M phase arrest in tumor cells (54,55). SAMC and DADS can inhibit the polymerization of tubulin and thus affect the function of the spindle, resulting in mitotic arrest (56). In addition, allicin induces cell cycle arrest in the cancer (11 studies) and colorectal cancer (9 studies). Our results indicated that garlic intake significantly reduces the risk of gastric cancer (OR=0.65, 95% CI=0.49-0.87, P<0.001) and colorectal cancer (OR=0.75, 95% CI=0.65-0.87, P<0.001), consistent with the epidemiological evidence supporting the correlation between garlic intake and a reduced risk of gastric and colorectal cancer. The results of the geographical subgroup analysis showed that a greater risk reduction occurs in the Asian region compared with other geographical regions. We suspect one of the possible reasons is that garlic consumption is higher in Asia, especially in China, where the habit of eating raw garlic leads to a higher consumption than other countries in the world (51,52). Some studies have also analyzed the effects of allium and onion on gastrointestinal tumors. We speculate that the active ingredients may be the same or similar to garlic, and that these foods may have a superimposed effect on gastrointestinal cancers (12,18,38,40,41). In addition, the European population may be under-represented since there was only one study conducted in Europe. Our meta-analysis incorporated the results of the latest research by Li et al (13) and summarized the recent studies. Although most of the included studies were retrospective case-control studies, lacking blinding and randomized control (53), we still found that garlic intake was associated with a reduced risk of gastric and colorectal cancer. Compared to the previous meta-analysis on the relationship between garlic and gastric and colorectal cancer by Fleischauer et al (28), our meta-analysis included more studies and conducted a subgroup analysis with a focus on garlic intake, resulting in more reliable conclusions. Due to the various dietary patterns in the different studies, we cannot exclude the effects of other factors, such as vegetable and fiber intake. Additionally, each study had different confounding factors, and most studies adjusted them, such as sex, age, and others. From the results of the subgroup analysis, it was shown that the intake of garlic can reduce the likelihood of gastric cancer compared with the non-intake of garlic. Although a previous meta-analysis by others showed that the protective effect of garlic on gastric and colorectal cancer may be overestimated (28), the results of the comprehensive analysis in this study indicated the preventive function of garlic in gastrointestinal tumors.

**Discussion**

This meta-analysis combined the results of 20 studies regarding the association of garlic consumption with gastric cancer. (A) Sensitivity analysis of garlic and gastric cancer. No significant differences were found among the studies. (B) Sensitivity analysis of garlic intake and colorectal cancer. The results of the sensitivity analysis showed that no articles exceeded the limits and there were no significant differences among the studies.
Garlic's organic sulfides, including DADS, DATS, SAMC, and allicin, can induce cell apoptosis through various mechanisms. First, these sulfides promote the release of cytochrome c from mitochondria, activating caspase 3 and caspase 9, and inducing apoptosis (23,56,58‑62). Second, DATS can activate the p53 pathway, resulting in the decreased expression of Bcl‑2 and increased expression of Bax (54,58,63‑65). SAMC and DATS significantly activate three pathways of the MAPKs pathway, including ERK, JNK, and p38 (63,64). Moreover, DATS can significantly upregulate the level of glycogen synthase kinase 3β (GSK3β) to increase the digestion of β‑catenin, indicating that DATS can inhibit the Wnt/β‑catenin pathway, which is a key component in the occurrence and development of tumors. DATS can also increase reactive oxygen species (ROS) production and activate the AMPK pathway (23,55). Allicin can reduce phosphorylated signal transducer and activator of transcription 3 (STAT3) to inhibit the STAT3 pathway, as well as activate Nrf2 and induce its translocation to the nucleus (66,67).

To summarize, DADS, DATS, SAMC, and allicin participate in tumor‑related biological processes through various mechanisms, eventually leading to apoptosis, cell cycle arrest, and migration inhibition in tumor cells. A medical compound containing active ingredients from garlics may exert potential tumor preventive or therapeutic effects through the above ‑ mentioned mechanisms in the human body, representing a novel antitumor treatment alternative.
This meta-analysis has the following limitations. i) Only a small set of randomized controlled trials are included in the date, most of which are case-control and cohort studies. Compared with randomized controlled trials, case-control and
cohort studies have more unaccounted parameters in blind control and follow-up, resulting in higher propensity of bias. ii) This meta-analysis included studies conducted in different countries since the 1990s. Not all studies were primarily based on onion vegetables, and there was inconsistent stratification among the studies. iii) Most of the included studies were conducted in China, where the incidence of gastric cancer is generally higher than the rest of the world. Moreover, garlic intake is relatively high in the diet of Chinese people. iv) Many studies did not control other diets, and the type of garlic consumption remains unstandardized. It is difficult to determine the minimum garlic intake for a tumor-protective effect. The minimum and maximum consumption levels varied greatly among the different studies.

The quantified F test showed that the included studies had significant heterogeneity, and Galbraith test suggested that some studies might be the sources. Therefore, we explored the possible cause for the heterogeneity. First, most of the included studies were retrospective studies with various confounding factors, and recall bias may have produced different results from the prospective studies. Second, most studies had collected data in the form of questionnaires instead of objective measurement. Third, studies conducted in Asia, especially in China, where garlic is a highly consumed food, may lead to certain bias on the results when pooled together with studies conducted in other places with much lower garlic consumption.

In summary, our meta-analysis provides strong evidence that garlic can reduce the risk of gastric and colorectal cancers. The conclusion was mainly based on case-control studies with many potential confounders, and further research is warranted to validate it.

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Availability of data and materials

The study was registered in PROSPERO (CRD42020179464).

Authors' contributions

HJL designed the review and meta-analysis. YYW and HJL conceived and wrote the review. YFW and DRL acquired and analysed the data. MYJ and PH analyzed and confirmed the integrity of the data found in the literature. YSW was involved in drafting the manuscript. All authors contributed to the analysis, reviewed the results and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Authors' information

ORCID: Huanjie Li, orcid.org/0000-0002-4997-0927; Yunshan Wang, orcid.org/0000-0003-3767-6728.

Competing interests

The authors declare that they have no competing interests.

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