

Original Research



Effects of garlic intake on cancer: a systematic review of randomized clinical trials and cohort studies

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OPEN ACCESS

Received: Mar 8, 2021

Revised: May 14, 2021

Accepted: Jul 21, 2021

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Funding

This research was supported by a grant (21162MFDS076) from Ministry of Food and Drug Safety in 2021 and partly supported by

ABSTRACT

BACKGROUND/OBJECTIVES: Due to the rapid increase of global cancer incidence and mortality and a high level of interest in cancer prevention, a systematic review of garlic intake and cancer risk is needed.

SUBJECTS/METHODS: We implemented a systematic review to examine the effects of varying levels of garlic intake on cancer. We conducted comprehensive literature searches in three electronic databases (MEDLINE, Embase, and Web of Science) for studies published between database inception and July or September of 2018. Two investigators independently screened abstracts and full-texts, extracted data, and assessed risk of bias (RoB). A total of one medium-quality randomized controlled trial (RCT) and 13 cohort studies graded as high RoB were included.

RESULTS: The 1-year follow-up results from a RCT showed that a significant decrease in the number and size of colorectal adenomas among participants with colorectal adenomas who received high-dose aged garlic extract (AGE) compared with those who received low-dose AGE ($P < 0.05$). The results of prospective observational studies provided inconsistent associations of colorectal cancer risk with garlic supplements and garlic intake as food.

CONCLUSIONS: In summary, the AGE was effective in reducing the number and magnitude of colorectal adenomas in one RCT, but there were inconsistent associations between garlic intake and colorectal cancer in cohort studies. Therefore, we could not draw a firm conclusion regarding the effects of garlic on cancer, because the current strength of evidence is inadequate due to a lack of number of high-quality RCTs.

Keywords: Garlic; cancer; systematic review

INTRODUCTION

Cancer incidence and mortality rates are increasing rapidly worldwide [1]. The World Health Organization (WHO) reported that 1 in 6 people, a total of 9.6 million, died due to cancer in 2018, and that cancer is the second leading cause of death worldwide [2]. Among cancers, lung cancer (1.76 million deaths), colorectal cancer (862,000 deaths), stomach

Cooperative Research Program for Agriculture Science and Technology Development (project No. PJ014536022021) Rural Development Administration, Republic of Korea.

Conflict of Interest

The authors declare no potential conflicts of interests.

Author Contributions

Conceptualization, Chung M, Lee HJ, Lee J; Data curation: Fu Z, Zhao N; Formal analysis: Chung M, Lee J; Funding acquisition: Lee HJ; Investigation: Fu Z, Zhao N, Choi J; Methodology, Chung M, Lee J; Project administration: Lee J; Supervision: Chung M, Lee HJ; Validation: Fu Z, Zhao N; Writing - original draft: Lee J, Choi J; Writing - review & editing: Chung M, Lee HJ.

cancer (783,000 deaths), liver cancer (782,000 deaths), and breast cancer (627,000 deaths) caused the most deaths in 2018 [2]. It has been reported that one-third of cancer deaths are associated with dietary risks and behaviors, such as a high body mass index, a low fruit and vegetable intake, a lack of physical activity, tobacco use, and alcohol use [2]. These results indicate that dietary habits are critical to cancer prevention.

Garlic (*Allium sativum* L.) is a perennial plant belonging to the Liliaceae, and has been widely cultivated and used as traditional medicine and seasoning and food for thousands of years [3]. Garlic contains more than 33 organic sulfur compounds, in addition to amino acids, vitamins, and micronutrients [4]. The major allyl sulfur content in freshly crushed or chopped garlic is allicin, which is unstable and breaks down rapidly to produce odorous oil-soluble diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and ajoene. The major allyl sulfur constituents in processed garlic, S-allylcysteine (SAC) and S-allylmercaptocysteine, are water soluble and formed by the process of natural aging bioconversion [5].

Garlic and its bioactive constituents have been shown to have many properties in *in vitro* or *in vivo* studies: anticancer, antithrombotic, antioxidant, anti-inflammatory, antibacterial, antifungal, immunomodulatory, cardiovascular protective, hepatoprotective, digestive system protective, antidiabetic, antiobesity, neuroprotective, and renal protective [6,7]. Particularly, anticancer effects of garlic may affect cancer cells by modulation of many pathways including alteration in carcinogen-metabolizing enzymes, cell cycle arrest, and induction of apoptotic cell death and suppression of oncogenic signal transduction pathways [8-10]. Although the beneficial effects of garlic intake against cancer have been reported in animal studies, benefits in human studies still remain controversial [11].

The Continuous Update Project (CUP) is the largest source of scientific evidence on cancer prevention of diet, weight, and exercise. The results from this CUP (2018) showed no conclusion was drawn due to very limited evidence supported a relation between garlic intake and risk of colorectal cancer [12]. Although there were a few systematic reviews conducted to investigate the effects of garlic intake on cancer, the researchers used a less reliable, and less valid assessment tool instead of the most commonly recommend tool, such as the Cochrane risk of bias tool for RCTs [4,8]. One meta-analysis of the epidemiological data on the association between garlic intake and cancer prevention did not include information on critical appraisal of study quality [13]. Another meta-analysis included only prospective cohort studies, but not RCTs [14]. Therefore, we aimed to conduct a systematic review to evaluate whether there is a causal relationship between garlic intake and cancer, following the rigorous methods outlined in the Cochrane handbook for systematic reviews including both RCTs and observational studies [15].

SUBJECTS AND METHODS

Data sources and searches

The searches for randomized controlled trials (RCTs) and observational studies, such as prospective cohort studies, related to cancer (surrogate and clinical outcome, including cancer-specific mortality) were performed in 3 databases: MEDLINE (from inception to July 1st week, 2018; search on July 17th, 2018), Embase (from inception to September 5th, 2018; search on September 5th, 2018), and Web of Science (from inception to September 5th, 2018;

search on September 5th, 2018). No language restriction was added. The complete search strategy is presented in **Supplementary Table 1**. Moreover, other articles were identified from the previously published systematic reviews and added to our study [16-18].

Study eligibility criteria

We included human intervention trials with a minimum duration of 4 weeks, as well as prospective observational studies (i.e., prospective cohort studies, nested case-control studies, and case-cohort studies). To be included, studies must have provided quantitative information on oral garlic intake from foods or dietary supplements. Studies not containing this quantitative information of garlic intake must have compared different doses of garlic intake (e.g., higher vs. lower doses) or compared the effect of garlic alone with that of a placebo or another active comparator. Finally, studies must have reported outcomes related to cancer, including all types of cancer incidence and mortality (i.e., a specific type of cancer, cancer-specific mortality, or surrogate of cancer risk).

Study selection process

The abstract and titles of all citations were independently screened by 2 investigators according to the established criteria. The abstract screening was performed in the open-source, online software Abstrackr by 2 investigators separately [19]. The full-text screening was performed independently according to the eligibility criteria by 2 investigators. Conflicts were resolved by group consensus. The study selection process is summarized in **Fig. 1**. Although no language restrictions were applied during the literature search, this systematic review did not identify any foreign language studies.

Data extraction and study quality assessment

Two investigators independently extracted data (e.g., study characteristics, risk ratio) from each included study by using standardized data extraction forms. Discrepancies were resolved by discussion between the two investigators or further group discussion. To assess the risk of bias (RoB) for each included study, we used validated tools—the Newcastle-Ottawa Scale (NOS) for prospective cohort studies [20] and the Cochrane RoB tool for randomized controlled trials [21]. For this study, we modified the study quality assessment tool of the NOS taking out ‘Demonstration That Outcome of Interest Was Not Present at Start of Study’ and ‘Was Follow-Up Long Enough for Outcomes to Occur’ from the original NOS because all included prospective studies were rated ‘low risk’ for these two questions. Instead, we added ‘adequate sample size and power’ and ‘selective outcome reporting’ questions. Therefore, the modified NOS finally consisted of 8 evaluation items (**Supplementary Table 2**):

(1) representativeness of the exposed cohort; (2) selection of the nonexposed cohort, (3) ascertainment of nutrient exposure, (4) control for important confounders, (5) adequate sample size and power, (6) outcome assessment, (7) completeness of cohort follow-up, and (8) selective outcome reporting. The Cochrane RoB tool consisted of 5 domains: (1) bias arising from the randomization process, (2) bias due to deviations from the intended intervention, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported result. Two investigators rated the RoB with 1 of 3 options: high, low, or unclear risk. Discrepancies were resolved by discussion between the 2 investigators.

Qualitative synthesis and data reporting

Due to large clinical heterogeneity, particularly the different types of garlic intake and various doses of garlic intake reported in the included studies, we performed a narrative synthesis instead of a meta-analysis. We reported our systematic review according to the Preferred

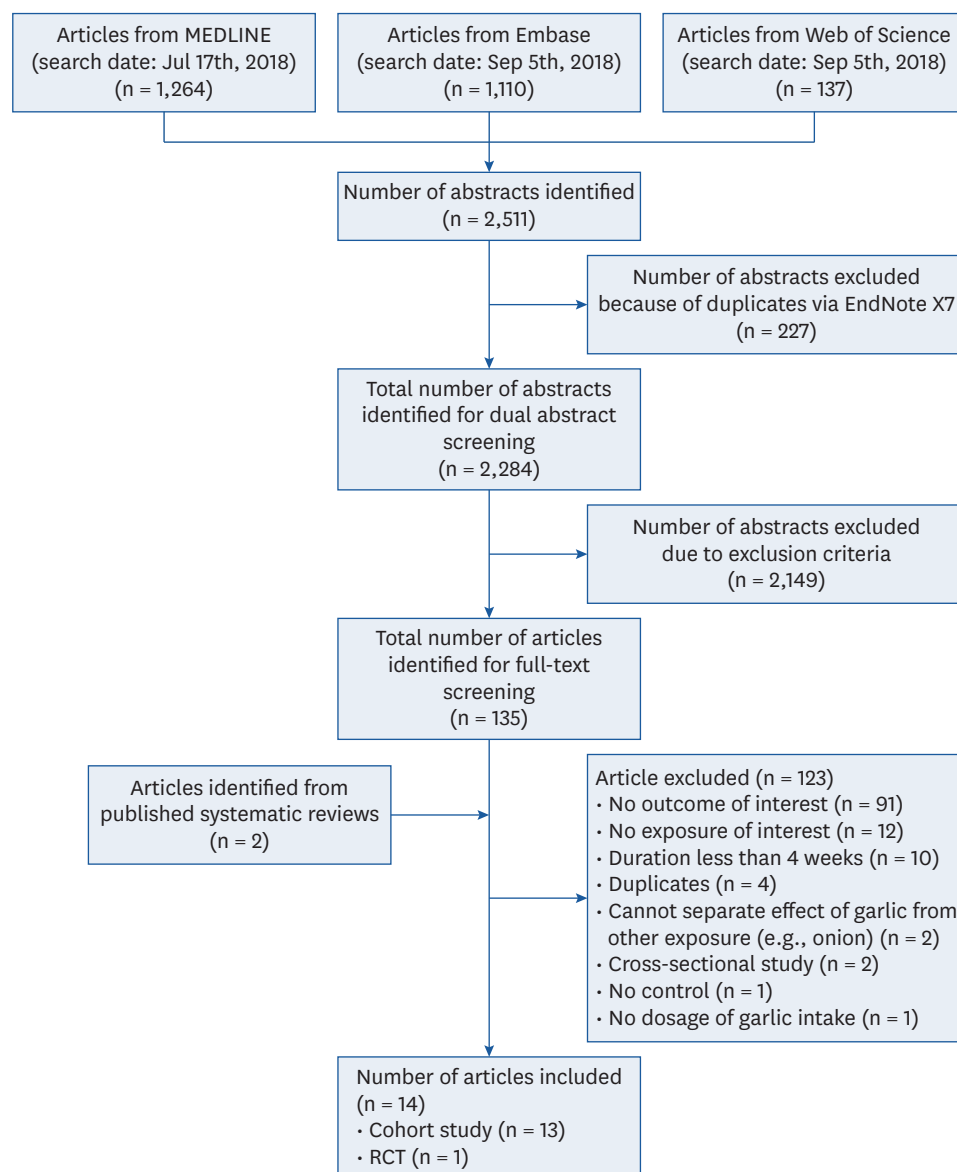


Fig. 1. Literature search and study selection process. RCT, randomized controlled trial.

Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [22]. We assessed the strength of evidence (SoE) for all outcomes by utilizing an evidence grading system employed by the American Diabetes Association (**Supplementary Table 3**) [23].

RESULTS

The initial search yielded 2,511 citations. Of these, we identified 2,284 unduplicated abstracts for dual abstract screening. Then, we screened 135 possibly relevant articles for full-text screening. Finally, we selected 14 articles (1 RCT and 13 cohort studies). **Fig. 1** shows the flow chart of the study selection process. **Tables 1** and **2** present the characteristics of the

Table 1. Characteristics of the included RCT

Author, Year [Reference]	Country	Male sex at enrollment (%)	Baseline age (yrs), mean ± SD	Baseline health status	Design/ duration	Garlic group		Comparison group		Outcome	Adverse events
						Sample size	Intervention	Sample size	Intervention		
Tanaka, 2006 [24]	Japan	72.97%	High-AGE, 57.6 ± 1.3; Low-AGE, 61.3 ± 2.0	Colorectal adenomas	12 mon	19	2.4 mL per capsule *3 capsules *2 times per day	18	0.16 mL per capsule *3 capsules *2 times per day	Incidence of adenomas, number of adenomas and total size of adenomas	1 had itchy back in high-AGE and 3 had eczema on the upper limbs, epigastric pain, and glossitis in low-AGE

RCT, randomized controlled trial; AGE, aged garlic extract.

Table 2. Risk of bias assessment for the included RCTs

Author, Year [Reference]	Bias arising from the randomization process	Bias due to deviations from the intended interventions	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported results	Overall bias
Tanaka, 2006 [24]	Some concerns	Low	Low	Low	Low	Moderate (= some concerns)

RCT, randomized controlled trial.

included RCTs and prospective observational studies (i.e., cohort and case-cohort studies), respectively. We present the results by the research questions, specifically the effects of garlic intake on colorectal cancer and other types of cancer. We summarized the findings of this RCT first, followed by the results of the prospective observational studies.

Garlic intake and colorectal cancer

RCTs

Only one RCT [24] met our inclusion criteria (Table 1). Participants (n = 51) with colorectal adenomas (i.e., precancerous lesions of the large bowel) were randomized to either high-dose aged garlic extract (AGE) (2.4 mL/day) or low-dose AGE (0.16 mL/day) for 12 mon. The number and size of colorectal adenomas were assessed via colonoscopy. Of the 51 participants, 37 patients completed the study (19 in the high-dose AGE group vs. 18 in the low-dose AGE group). The results of this RCT showed that high-dose AGE significantly suppressed both the number and total size of colorectal adenomas compared to low-dose AGE after 12 months of intervention ($P < 0.05$). The overall RoB of this RCT was graded as moderate because of some concerns regarding bias arising from the randomization process (Table 2).

Prospective observational studies

We included 7 prospective observational studies (6 cohort studies and 1 case-cohort study) [25-31] in the analysis of garlic intake and risk of colorectal cancer (Table 3). These studies included 3 studies [29-31] of total colorectal cancer, 4 studies [25-28] of colon cancer, and 1 study each of rectal cancer [27-31], proximal colon cancer [26,31], and distal colon cancer [26,31]. The majority of the included studies (6 of 7 studies) were prospective cohort studies conducted in the U.S., and only one case-cohort study was conducted in the Netherlands. The follow-up duration of the included studies ranged from 3.3 to 24 yrs. The types of garlic exposure were only garlic intake from food sources for 3 studies, only garlic supplements for 2 studies, and garlic from both food and supplements for 2 studies. Only male participants were included for 4 of the 7 studies. The number of participants ranged from 35,210 to 173,229 participants across the 6 prospective cohort studies. The overall RoB was graded as moderate for all 7 studies, specifically due to use of insufficient methods to estimate accurate and usual dietary intake (e.g., food frequency questionnaire or only a single 24 h) to ascertain garlic exposure and inadequate information for statistical power (Table 4).

Table 3. Characteristics of the included cohort studies (n = 13)

Author, Year [Reference]	Study name	Country	Study design	No. of subjects	Male sex at enrollment (%)	Baseline age	Duration of follow-up (yrs)	Exposure	Comparisons	Exposure assessment	Outcome	Nutrients	Demo-graphics	Anthropo-metrics	Medical conditions	Lifestyles
Dorant, 1994 [32]	The Netherlands Cohort Study	Netherlands	Case-cohort	484 cases, 3,122 controls	54.2%	Range, 55-69	Mean, 3.3	Garlic supplements	Use vs. no use	150-item semiquantitative	Lung cancer	X	X	X	X	X
Giovannucci, 1994 [25]	The Health Professional Follow-up Study Cohort	U.S.	Cohort	205 cases, 47,949 total	100%	Range, 40-75	Mean, 6	Garlic intake	≥ 2 servings vs. 0 servings per week	Semi-quantitative FFQ	Colon cancer	X	X	X	X	X
Steinmetz, 1994 [26]	The Iowa Women's Health Study	U.S.	Cohort	212 cases, 35,216 total	0	Mean, 61.7	Mean, 5	Garlic intake	0, 0.5, ≥ 1.0 serving per week	The Willett semi-quantitative FFQ	Colon cancer, proximal colon cancer, distal colon cancer	X	X	X	X	X
Dorant, 1995 [33]	The Netherlands Cohort Study	Netherlands	Case-cohort	468 cases, 1,812 controls	0	Mean, 61.5	3.3	Garlic supplements	Use vs. no use	150-item semi-quantitative FFQ	Breast cancer	X	X	X	X	X
Dorant, 1996 (a) [27]	The Netherlands Cohort Study	Netherlands	Case-cohort	478 cases, 3,346 controls	49.58%	Range, 55-69	Mean, 3.3	Garlic supplements	Use vs. no use; Use vs. other supplements	150-item semi-quantitative FFQ	Colon cancer; rectal cancer	X	X	X	X	X
Dorant, 1996 (b) [34]	The Netherlands Cohort Study	Netherlands	Case-cohort	155 cases, 3,346 controls	36.59%	Range, 55-69	Mean, 3.3	Garlic supplements	Use vs. no use; Use vs. other supplements	150-item semi-quantitative FFQ	Stomach cancer	X	X	X	X	X
Sellers, 1998 [28]	The Iowa Women's Health Study	U.S.	Cohort	241 cases, 35,216 total	0	Mean, 61.7	Mean, 10	Garlic intake	0, ≤ 1, > 1 servings per week	127-item FFQ	Colon cancer	X	X	X	X	X
Satia, 2009 [29]	The VITAL (Vitamins And Lifestyle) cohort	U.S.	Cohort	665 lung cancer cases, 428 colorectal cancer cases, 77,719 total	Lung: 48.04%; Colon: 48.01%	Mean ± SD, Lung: 67.2 ± 6.6; Colon: 66.3 ± 6.7; No disease: 61.9 ± 7.4	Mean ± SD, 5.0 ± 1.01	Garlic supplements	Use (any use in the past 10 years) vs. no use	Questionnaire	Lung cancer, colorectal cancer	X	X	X	X	X
Brasky, 2011 [35]	The VITAL (Vitamins And Lifestyle) cohort	U.S.	Cohort	1,602 cases, 35,239 total	100%	Range, 50-79	Median, 6.1	Garlic supplements	Use vs. no use	Questionnaire	Prostate cancer	X	X	X	X	X
Walter, 2011 [36]	The VITAL (Vitamins And Lifestyle) cohort	U.S.	Cohort	588 cases, 66,227 total	49.20%	Mean ± SD, 61.5 ± 7.4	Mean ± SD, 6.5 ± 1.8	Garlic supplement (from single supplements (and mixtures other than multivitamins) plus multivitamins)	High use vs. low use vs. no use	A 24-page self-administered, sex-specific questionnaire	Hematologic malignancy	X	X	X	X	X
McCullough, 2012 [30]	The Cancer Prevention Study II Nutrition Cohort	U.S.	Cohort	1,130 cases, 99,700 total	42.95%	Mean range, 66.9-70.7	Mean, 7	Garlic intake; garlic supplements	< 1 clove per month, 1 clove per month, > 1 clove per month; continuous garlic intake (each clove/week); use vs. no use	152-item modified Willett FFQ	Colorectal cancer	X	X	X	X	X

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Table 3. (Continued) Characteristics of the included cohort studies (n = 13)

Author, Year [Reference]	Study name	Country	Study design	No. of subjects	Male sex at enrollment (%)	Baseline age	Duration of follow-up (yrs)	Exposure	Comparisons	Exposure assessment	Outcome	Nutrients	Demo-graphics	Anthropo-metrics	Medical conditions	Medica-tions	Lifestyle
Meng, 2013 [31]	The Nurses' Health Study and the Health Professionals Follow-Up Study	U.S.	Cohort	1,339 colorectal cancer cases, 1,054 colon cancer cases, 634 proximal colon cancer cases, 397 distal colon cancer cases, 285 rectal cancer cases, 121,700 total in NHS; 1,029 colorectal cancer cases, 811 colon cancer cases, 345 proximal colon cancer cases, 314 distal colon cancer cases, 218 rectal cancer cases, 51,529 total in HPFS	0 in NHS, 100% in HPFS	30-55 in NHS; 40-75 in HPFS	24 in NHS, 22 in HPFS	Garlic intake; garlic supplements	< 1 clove per month, 1-3 cloves per month, 1 clove per week, 2-4 cloves per week, 5-6 cloves per week, ≥ 1 clove per day; use vs. no use	Semiquantitative FFQ with up to 130 foods	Colorectal cancer, colon cancer, proximal colon cancer, distal colon cancer, rectal cancer	X	X	X	X	X	X
Kim, 2018 [37]	The Nurses' Health Study and the Health Professionals Follow-Up Study	U.S.	Cohort	292 cases in NHS and HPFS; 121,700 total in NHS; 51,529 total in HPFS	0 in NHS, 100% in HPFS	30-55 in NHS; 40-75 in HPFS	30 in both NHS and HPFS	Garlic intake	0-1 clove per week, 1-4 cloves per week, ≥ 5 cloves per week	Semiquantitative FFQ	Gastric cancer	X	X	X	X	X	X

FFQ, food frequency questionnaire; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

Table 4. Risk of bias assessment for the included cohort studies (n = 13)

Author, Year [Reference]	Outcome	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of nutrient exposure	Control for important confounders	Adequate sample size and power	Outcome assessment	Completeness of cohort follow-up	Selective outcomes reporting	Overall RoB
Dorant, 1994 [32]	Lung cancer	Low	Low	High	Low	Unclear	Low	Low	Low	Moderate
Giovannucci, 1994 [25]	Colon cancer	Low	Low	High	Low	Unclear	Low	Low	Low	Moderate
Steinmetz, 1994 [26]	Colon cancer, proximal colon cancer, distal colon cancer	Low	Low	High	Low	Unclear	Low	Low	Low for all outcomes	Moderate
Dorant, 1995 [33]	Breast cancer	Low	Low	High	Low	Unclear	Unclear	Low	Low	Moderate
Dorant, 1996 (a) [27]	Colon cancer; rectal cancer	Low	Low	High	Low	Unclear	Low	Low	Low for both outcomes	Moderate
Dorant, 1996 (b) [34]	Stomach cancer	Low	Low	High	Low	Unclear	Low	Unclear	Low	Moderate
Sellers, 1998 [28]	Colon cancer	Low	Low	High	Low	Unclear	Low	High	Low	Moderate
Satia, 2009 [29]	Lung cancer, colorectal cancer	Low	Low	High	Low for both outcomes	Unclear	Low for both outcomes	Low	Low for both outcomes	Moderate
Brasky, 2011 [35]	Prostate cancer	Low	Low	High	Low	Unclear	Low	Low	Low	Moderate
Walter, 2011 [36]	Hematologic malignancy	Low	Low	High	Low	Unclear	Low	Low	Low	Moderate
McCullough, 2012 [30]	Colorectal cancer	Low	Low	High	Low	Unclear	Low	Low	Low	Moderate
Meng, 2013 [31]	Colorectal cancer, colon cancer, proximal colon cancer, distal colon cancer, rectal cancer	High	Low	High	Low	Unclear	Low	Low for HPFS, high for NHS	Low for all outcomes	Moderate
Kim, 2018 [37]	Gastric cancer	High	Low	High	Low	Unclear	Low	Low	Low	Moderate

RoB, risk of bias; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

Colorectal cancer

Three cohort studies reported associations between garlic intake and colorectal cancer risk (Table 5) [29-31]. Three studies investigated garlic intake from different sources: 1 study each investigated garlic intake from food sources [31]; garlic supplements [29], and garlic intake from both food source and supplements [30]. Two studies reporting garlic intake from garlic supplements showed consistent results. One study reported that any garlic supplement use in the past 10 years significantly increased the risk of colorectal cancer compared with that of nonusers of garlic supplements (relative risk [RR] = 1.35, 95% confidence interval [CI] = 1.01, 1.81) [29]. The other study showed that past use of garlic supplements had a significant effect on total colorectal cancer risk compared with that in the never-user group (RR = 1.45, 95% CI = 1.02, 2.07) [30]. Two studies reporting garlic intake from food sources showed no significant associations between garlic intake and the risk for developing colorectal cancer [30,31].

Colon cancer

Three cohort studies and one case-cohort study [25-28] examined associations between garlic intake and colon cancer (Table 5). The three cohort studies examined garlic intake from food sources, and the case-cohort study investigated garlic supplements. All 3 cohort studies

Table 5. Colorectal cancer risk stratified by garlic intake

Author, Year [Reference]	Cancer outcome	Subgroup	Follow-up	Garlic intake comparison	No.	Adjusted RR	95% CI
Dorant, 1996 (a) [27]	Colon cancer		3.3 yrs	Garlic suppl vs. no suppl	31 vs. 205	1.26	(0.84, 1.91)
	Colon cancer			Exclusively garlic suppl vs. no suppl	16 vs. 205	1.36	(0.79, 2.35)
	Rectum cancer		3.3 yrs	Garlic suppl vs. no suppl	12 vs. 126	0.77	(0.41, 1.46)
	Rectum cancer			Exclusively garlic suppl vs. no suppl	9 vs. 126	1.28	(0.63, 2.60)
Giovannucci, 1994 [25]	Colon cancer		6 yrs	Garlic intake ≥ 2 servings vs. 0 serving per week	NR	0.77	(0.51, 1.16)
Steinmetz, 1994 [26]	Colon cancer		5 yrs	Garlic intake 0.5 servings vs. 0 serving per week	NR	1.07	(0.77, 1.05)
	Colon cancer			Garlic intake ≥ 1 servings vs. 0 serving per week	NR	0.68	(0.46, 1.02)
	Proximal colon cancer			Garlic intake 0.5 servings vs. 0 serving per week	NR	1.31	(0.79, 2.22)
	Proximal colon cancer			Garlic intake ≥ 1 servings vs. 0 serving per week	NR	1.00	(0.56, 1.79)
	Distal colon cancer			Garlic intake 0.5 servings vs. 0 serving per week	NR	0.85	(0.53, 1.36)
	Distal colon cancer			Garlic intake ≥ 1 servings vs. 0 serving per week	NR	0.52	(0.30, 0.93)
Sellers, 1998 [28]	Colon cancer	No family history	10 yrs	Garlic intake < 1 serving vs. 0 serving per week	69 vs. 146	1.10	(0.70, 1.50)
	Colon cancer	No family history		Garlic intake > 1 servings vs. 0 serving per week	26 vs. 146	1.20	(0.80, 1.90)
	Colon cancer	Positive family history		Garlic intake < 1 serving vs. 0 serving per week	69 vs. 146	0.60	(0.50, 1.70)
	Colon cancer	Positive family history		Garlic intake > 1 servings vs. 0 serving per week	26 vs. 146	1.00	(0.40, 2.50)
Satia, 2009 [29]	Colorectal cancer			Any garlic suppl use in the past 10 year vs. non-user		1.35	(1.01, 1.81)
McCullough, 2012 [30]	Colorectal cancer		7 yrs	Garlic intake each clove per week		0.99	(0.96, 1.03)
	Colorectal cancer			Garlic suppl current use vs. never use	37 vs. 694	1.03	(0.74, 1.44)
	Colorectal cancer			Garlic suppl past use vs. never use	33 vs. 694	1.45	(1.02, 2.07)
Meng, 2013 [31]	Colorectal cancer		24 yrs	Garlic intake 1 clove per week vs. < 1 clove per month	227 vs. 283	1.07	(0.89, 1.27)
	Colorectal cancer			Garlic intake ≥ 1 clove per day vs. < 1 clove per month	78 vs. 283	1.21	(0.94, 1.57)
	Colorectal cancer		22 yrs	Garlic intake 1 clove per week vs. < 1 clove per month	127 vs. 400	0.93	(0.76, 1.14)
	Colorectal cancer			Garlic intake ≥ 1 clove per day vs. < 1 clove per month	35 vs. 400	1.00	(0.71, 1.42)

RR, relative risk; CI, confidence interval; NR, not reported.

examining garlic intake from food sources reported no significant associations between garlic intake and colorectal cancer [25,26,28]. One case-cohort study reported that garlic supplement users had a significantly increased risk of developing colon cancer compared with nonusers (RR = 1.45, 95% CI = 1.02, 2.07) [27].

Rectal cancer

One case-cohort study reported the relationship between garlic supplement intake and rectal cancer [27]. This study showed non-significant association between garlic supplement intake and the risk of rectal cancer (Table 5) [27].

Proximal colon cancer

One cohort study examined the association between garlic intake from food sources and proximal colon cancer, and showed a nonsignificant relationship between garlic intake and the risk of proximal colon cancer (Table 5) [26].

Distal colon cancer

One cohort study investigated the relationship between garlic intake from food sources and distal colon cancer [26]. This study reported that ≥ 1 serving garlic per week significantly decreased the risk of distal colon cancer (RR = 0.52, 95% CI = 0.30, 0.93) (Table 5) [26].

Other cancers (lung cancer, stomach cancer, prostate cancer, breast cancer, and hematologic malignancy)

Prospective observational studies

Three cohort and 3 case-cohort studies [29,32-37] investigated the associations between garlic intake and other types of cancer (**Table 6**). There were 2 studies each of lung cancer and stomach cancer. Additionally, there was only 1 study each of prostate cancer, breast cancer, and hematologic malignancy.

Lung cancer

One cohort and one case-cohort studies examining the relationship between garlic intake and lung cancer showed inconsistent results (**Table 6**) [29,32]. One study showed that the exclusive use of garlic supplements significantly increased the risk of lung cancer [32]. The other study reported a nonsignificant relationship between garlic supplement intake and lung cancer [29].

Stomach cancer

One cohort and one case-cohort studies examined the associations between garlic intake from food sources or supplements and stomach cancer (**Table 6**) [34,37]. Both studies showed a nonsignificant relationship between garlic intake and the risk of developing stomach cancer [34,37].

Hematologic malignancy, breast cancer, and prostate cancer

One cohort study asserted that high use of garlic supplements (≥ 4 days per week) significantly decreased the risk of hematologic malignancy compared with that of nonusers (hazard ratio = 0.55; 95% CI = -0.34, 0.87) (**Table 6**) [36]. Additionally, a few studies found nonsignificant relationships between garlic supplement intake and the risk of breast cancer [33] and prostate cancer [35].

Overall SoE

We graded the overall SoE, and it was inadequate for the causal effects of garlic intake on colorectal cancer, lung cancer, and stomach cancer (**Table 7**).

Adverse events

The one included RCT of garlic supplements [24] identified adverse events. One participant in the high-dose AGE group had itching on the back, and three participants in the low-dose AGE group reported eczema on the upper limbs, glossitis, and epigastric pain.

Table 6. Other types of cancer risk stratified by garlic intake

Author, Year [Reference]	Cancer outcome	Follow-up	Garlic intake	No.	Adjusted RR	95% CI
Dorant, 1994 [32]	Lung cancer	3.3 yrs	Garlic suppl vs. no suppl	48 vs. 419	1.22	(0.81, 1.86)
	Lung cancer		Exclusively garlic suppl vs. no suppl	29 vs. 419	1.78	(1.08, 2.92)
Dorant, 1995 [33]	Breast cancer	3.3 yrs	Garlic suppl vs. no suppl	24 vs. 305	0.75	(0.41, 1.38)
Dorant, 1996 [34]	Stomach cancer	3.3 yrs	Exclusively garlic suppl vs. no suppl	9 vs. 118	1.27	(0.61, 2.64)
	Stomach cancer		Garlic + any other suppl vs. any other suppl	5 vs. 20	1.28	(0.45, 3.66)
Satia, 2009 [29]	Lung cancer	5 yrs	Any garlic suppl use in the past 10 year vs. no use	80 vs. 582	1.05	(0.83, 1.34)
Brasky, 2011 [35]	Prostate cancer	6.1 yrs	Any garlic suppl use in the past 10 year vs. non-user	190 vs. 1,411	1.00	(0.85, 1.17)
Walter, 2011 [36]	Hematologic malignancy	6.5 yrs	Low use garlic suppl vs. none	38 vs. 523	1.07	(0.76, 1.51)
	Hematologic malignancy		High use garlic suppl vs. none	24 vs. 523	0.55	(0.34, 0.87)
Kim, 2018 [37]	Gastric cancer	30 yrs	Garlic intake 1-4 gloves per week vs. never	45 vs. 31	0.81	(0.50, 1.31)
	Gastric cancer		Garlic intake ≥ 5 gloves per week vs. never	18 vs. 31	1.34	(0.72, 2.47)
	Gastric cancer	30 yrs	Garlic intake 1-4 gloves per week vs. never	46 vs. 48	0.98	(0.71, 1.36)
	Gastric cancer		Garlic intake ≥ 5 gloves per week vs. never	13 vs. 48	1.39	(0.89, 2.17)

RR, relative risk; CI, confidence interval.

Table 7. SoE grading: garlic intake by outcome¹⁾

Outcome	No. of studies [Reference]		SoE grade	Explanation
	RCTs	Observational studies		
Colorectal cancer	1 [24]	3 [29-31]	Inadequate	Only 1 RCT was rated as having a moderate RoB; Three cohort studies that were rated as having a moderate RoB presented inconsistent findings.
Colon cancer	n/a	4 [25-28]	Inadequate	No RCT; Three cohort studies and one case-cohort studies that were rated as having a moderate RoB presented inconsistent findings.
Rectal cancer	n/a	1 [27]	Inadequate	No RCT; Only 1 case-cohort study was rated as having a moderate RoB
Proximal colon cancer	n/a	1 [26]	Inadequate	No RCT; Only 1 cohort study was rated as having a moderate RoB
Distal colon cancer	n/a	1 [26]	Inadequate	No RCT; Only 1 cohort study was rated as having a moderate RoB
Lung cancer	n/a	2 [29,32]	Inadequate	No RCT; One cohort and one case-cohort cohort studies that were rated as having a moderate RoB showed inconsistent findings.
Stomach cancer	n/a	2 [34,37]	Inadequate	No RCT; One cohort and one case-cohort cohort studies that were rated as having a moderate RoB showed inconsistent findings.
Prostate cancer	n/a	1 [35]	Inadequate	No RCT; Only 1 cohort study was rated as having a moderate RoB
Breast cancer	n/a	1 [33]	Inadequate	No RCT; Only 1 cohort study rated as having a moderate RoB
Hematologic malignancy	n/a	1 [36]	Inadequate	No RCT; Only 1 cohort study was rated as having a moderate RoB

SoE, strength of evidence; RCT, randomized controlled trial; RoB, risk of bias; n/a, not applicable.

¹⁾The SoE grading scheme is presented in **Supplementary Table 2**.

DISCUSSION

This systematic review identified insufficient evidence to draw conclusions for the causal relationship between garlic intake and cancer. Only one small RCT was identified, and the included cohort studies presented large methodological heterogeneity (i.e., follow-up duration, types of garlic intake: supplements, food, or both, assessment tool of garlic exposure, and various comparison groups) hindering the comparability of the results.

Up to now, garlic has been reported that has favorable effects against cancer in vitro and in animal studies. Their major compounds were well known as allicin, ajoene, DAS, DADS, and DATS. Among them, DAS is the major ingredient of cooked garlic which comprise about 60% of garlic oil [38]. The mechanism of anticancer effects of garlic ingredients has been revealed through the animal and human cancer cell line experiments. Previous research have reported that DAS can decrease testosterone and N-methyl-N-nitrosourea (MNU) induced carcinogenesis in the prostate gland of rats [39], and dwindle the incidence of tumor formation in MNU-induced carcinogenesis in mammary glands through inhibition of DNA alkylation as well as formation of two nitrosamine-related DNA adducts; O(6)-methylguanine and N(7)-methylguanine [40]. DADS reduced benzo[a]pyrene-induced carcinogenesis in human hepatoma cells through inhibition of the cytochrome P450 activity [41]. Several studies have revealed that the antiproliferative property of DADS in cultured human colon tumor cells (HCT-15) relative to its ability to decrease the proportion of cells in the G1 phase and increase the proportion of cells in the G2/M phase. All of these results suggested that the DADS compound can exert antiproliferative effects through cell cycle arresting in mitosis, which leads to apoptosis [42]. Additionally, DADS increases reactive oxygen species and oxidative stress that can induce apoptosis in many types of mammalian tumor cells [43]. The mechanisms by which DAD, DADS, the major components of garlic, elicit anti-cancer activity include histone acetylation, endoplasmic reticulum stress, and the Fas-mediated cell death pathway [44]. In this systematic review, we could not provide clear scientific conclusions regarding the effects of garlic on cancer because analytical and process information of garlic supplement or garlic intake were not reported in the included studies. The amount of

individual garlic component (e.g., allicin) could be affected by various factors such as types of garlic, cooking, smashing, storage, and method of preservation.

We must concede that despite the many studies that have done, the conclusions of this present review do not differ greatly from that of a previous one done almost two decades ago. Fleischauer and Arab [45] reported in 2001 the relationship between garlic intake and cancer incidence in 19 case-control or cohort studies. This report stated that only a few retrospective case-control studies showed inverse association of garlic intake with stomach and colorectal cancer, but the included cohort studies did not show any significant relationship for stomach and colorectal cancers. Similar to what we found in this systematic review, the authors pointed out a limited number of studies, inappropriate adjustment for potential confounding factors, and inaccurate measure of garlic intake would make it hard to come to a reliable conclusion.

In prospective observational studies, we found contradictory results on the relationship between the cancer outcomes and various types of garlic intake (i.e., food and supplement). As for colorectal cancer, 2 studies [29,30] showed that the intake of garlic supplements increased the risk of colorectal cancer, while 2 studies [30,31] did not show significant associations between garlic intake from food sources and the risk of colorectal cancer. In the case of colon cancer, one study showed that the intake of garlic supplementation increased the risk of colon cancer [27], while 3 studies revealed that there was no significant relationship between the garlic intake from food sources and the risk of colon cancer [25,26,28]. Additionally, rectal cancer was not significantly related with the intake of garlic supplement [27]. However, garlic intake from food sources significantly decreased the risk of distal colon cancer [26]. Therefore, we found the varying relationship between garlic intake and colon cancer may vary depending on how garlic is consumed and where colorectal cancer occurs. In the case of lung cancer, one study [32] showed that garlic supplementation increased the risk of lung cancer, while another study [29] revealed no significant association between garlic supplementation and the risk of lung cancer. From the results of this study, it is speculated that it is best to consume an appropriate amount of garlic in the form of food, not supplements. Generally, our body would absorb and metabolize nutrients from complex mixtures in foods. Thus, if the nutrients are consumed in a purified or concentrated supplements form, they can easily interfere with the absorption of other nutrients from foods consumed at the same time [46]. Therefore, it is safe and recommended to eat garlic as a food at a daily table.

The strength of this systematic review is that we have used robust study eligibility criteria for the study designs. However, this systematic review has a few limitations. All included observational studies have a high risk of bias in ascertainment of nutrient exposure. The included observational studies employed either food frequency questionnaire to assess dietary intake of garlic or specific questionnaire to measure consumption of garlic supplements. FFQs have inherent measurement errors in cohort studies [47], while multiple 24-hour dietary recalls or diet diaries are considered as a more accurate instrument [48]. In addition, the included studies did not provide information on how the garlic dosages were prepared. The concentration of allicin intake from garlic supplements and garlic foods consumption depends on a set of variables, including moisture content, temperature conservation, type of garlic used, storage conditions [49]. When clinical studies do not determine allicin bioavailability from the garlic samples used [50], it is difficult to correctly judge the final composition of garlic samples. Taken into consideration of the limitations in this systematic review, we suggest future studies to employ a more objective measurement of

garlic consumption, to overcome the limitations of using FFQs. There are several promising biomarkers for garlic consumption such as S-allyl-mercapturic acid, allyl methyl sulfide, allyl methyl sulfoxide, allyl methyl sulfone, and SAC [51]. Using biomarkers to quantify dietary intake will enable future systematic reviews to correctly capture and compare the effect of garlic intake in all included studies.

In conclusion, one RCT showed that the aged garlic extract significantly decreased the size and number of colorectal adenomas, while several cohort studies indicated inconsistent relationships between garlic intake and colorectal cancer. We determined that the SoE was inadequate for the effects of garlic intake on cancers due to insufficient number of good-quality RCTs. We recommend that more prospective cohort studies, from the countries to have population with higher intake of garlic, such as Italia and South Korea, are needed to be included for the future systematic reviews.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Search strategy

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Supplementary Table 2

Detailed instructions of the modified Newcastle-Ottawa Scale (NOS)¹⁾ for cohort studies

[Click here to view](#)

Supplementary Table 3

Strength of evidence grading system¹⁾

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