

EFFECT OF GARLIC IN GASTRIC CANCER PROGNOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract – Objective: The fourth most common cancer, which is the second cause of death throughout the world, is gastric cancer. Different factors such as the environment and genetics may contribute to its etiology. One of the most recommended approaches to gastric cancer prevention is the consumption of allium vegetables and garlic, as a member of this family, was considerable from ancient times to treat various disorders. We undertook a systematic review and meta-analysis to determine the prognostic effect of garlic on gastric cancer.

Materials and Methods: In this systematic review and meta-analysis study, we searched for reports on the effect of garlic on gastric cancer prognosis to identify eligible studies up to June 30, 2018, in databases of PubMed, Web of Science, Scopus and Google-Scholar. Heterogeneities were assessed using I-square test. Prevalence and CI 95% were calculated using a fixed effects model. STATA version 13.1 software was used for all statistical analysis.

Results: Of the 115 studies found, five studies involving 16013 patients were included in our meta-analysis. Pooled analysis indicated a significant relation ($p=0.007$) between garlic intake and gastric cancer mortality. Moreover, the analysis showed that mortality risk among patients with garlic intake was 4% less than other patients and hazard ratio in patients with gastric cancer who took garlic was 46% less than the control group.

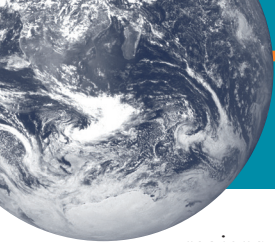
Conclusions: In this systematic review and meta-analysis, we found that the garlic intake in high doses could have a reducing effect on gastric cancer mortality. Hence, due to the efficacy of garlic consumption, its affordable status and no proven side effects, it is recommended to be used as part of our daily meal.

KEYWORDS: Stomach cancer, *Allium sativum*, *Allitridum*, Gastric neoplasm.

INTRODUCTION

Gastric Cancer (GC) is the fourth most common cancer and the second cause of death related to the cancers throughout the world¹. Approximately 90% of GCs are adenocarcinoma, which were derived from the glands of the surface layers or the mucus of the stomach². Various GC adenocarcinomas were categorized into two histological types of intestinal and

diffuse by Lauren's classification³. About 990,000 people were diagnosed with GC annually and about 738,000 of them losing their lives¹. The incidence of GC varies among men and women and between countries. The incidence rate for males is 2 to 3 times higher than in females^{1,2}. Regarding distribution pattern, over 70% of new cases occur in developing countries. In addition, the lowest rates of incidence and mortality are found in North America and most



regions of Africa and the highest incidence and mortality was identified in Asia, South America, Eastern Europe, less developed areas, WHO Western Pacific region and regions with medium levels of human development index^{4,5}. The incidence of GC has declined in many parts of the world over the last 50 years⁶⁻⁸. There has been a significant development in the balanced 5-year survival rate for this malignancy since the 1970s and the average global survival rate of 5 years in most regions of the world is about 20%^{9,10}. Tumor extent including involvement of nodal and extension of a tumor beyond the stomach wall as well as tumor stage were associated with a prognosis of GC patients. Moreover, factors such as prognostic serum markers, serum carcinoembryonic antigen (CEA) levels and prognostic tissue factors (e.g. HER1, HER2, p53, EGFR, COX-2, beta-catenin, etc.) are valuable prognostic molecular markers for GC diagnosis¹¹. GC is a multi-factorial disease that environmental and genetic factors contribute to its etiology. Some of these risk factors include gender (especially male), age (older ages), *Helicobacter pylori* (*H. Pylori*), radiation, family history, smoking, smoked foods, salty foods, lack of consumption of fruits and vegetables, consumption of antioxidant, nonsteroidal anti-inflammatory drugs, statins, obesity, physical activity, and gastroesophageal reflux disease². On behalf of GC prevention, there are two approaches; reducing the incidence of GC as a primary prevention or identifying and treating the malignancies at the early stages¹². There are some primary prevention approaches such as smoking cessation, reducing salt intake¹³, increasing fruits and vegetables consumption, eradication of *H. Pylori* (the main cause of gastric cancer)¹⁴, and NSAIDs and statins intake^{15,16}. According to previous studies, it is demonstrated that *allium* vegetables and their related sulfur components have a preventive chemical effect, especially on gastric cancer¹⁷⁻¹⁹. One of the most widely used *allium* vegetables that were considered from thousands of years ago to treat different diseases is *Allium sativum* (from the *L. fam. Alliaceae*), which we knew as garlic. The use of garlic for medicinal purposes dates back to 1550 BC and its drawings were discovered 3700 BC on the graves of Egyptians. Historically, it is used for various purposes such as motivational supplements for battles, as a protection for snakebites and crocodiles, belief of magical properties, heart disorders, headaches, improving sexual performance, antibacterial and antifungal properties, and malignancies^{20,21}. Moreover, some new properties of garlic including anti-inflammatory, anti-thrombotic, reduction of cholesterol, anti-oxidant effects were observed in recent studies and indicated that *allium* vegetables can have a reduction effect on the risk of several malignancies such as gastric cancer, colorectal cancer, lung cancer, breast cancer and prostate cancer^{19,22,23}. According to

our searching, we found no review study on the prognostic effect of garlic on gastric cancer; thus, we designed the present systematic review and meta-analysis to prove the new analytical results regarding the role of garlic in gastric cancer prognosis.

MATERIALS AND METHODS

SEARCH

In the present systematic review and meta-analysis, we performed a search strategy for relevant English publications through the databases until June 30, 2018. The search strategy includes (((Neoplasm AND stomach) OR "Stomach Neoplasm" OR "Gastric Neoplasm" OR (neoplasm AND gastric) OR "cancer of stomach" OR "Stomach Cancer" OR "Gastric Cancer" OR (cancer AND gastric) OR (cancer AND stomach) OR "cancer of the stomach")) AND (garlic OR "Allium sativum")) AND (fatality OR mortality OR death OR metastasis OR metastases). The search was limited to title/abstract/keywords in Scopus, PubMed, Web of Science and title in Google-Scholar. All references, exported to the EndNote software for duplication detection.

CRITERIA FOR INCLUDING STUDIES

All papers, which found through the search strategy, were screened by two researchers and scanned by title and abstract for making a decision about inclusion or exclusion. According to inclusion criteria, all English original studies that included the rate of mortality or hazardous ratio or if both of them could be calculated by the paper data regarding garlic consumption as an only approach of *allium* vegetables against GC were entered the meta-analysis. Exclusion criteria included the other types of research that could not support our requirement data, studies that did not separate garlic from other *allium* vegetables, and studies with insufficient information for any reason. Our data extraction checklist included author names, date, number of cases and controls, number of deaths among cases and controls, *p*-value that calculated for garlic effects against GC and hazard ratio. At the end of the search, 115 references were found. Of all obtained articles, 61 articles were unrelated to our purpose, 36 duplicated studies were found using Endnote software, and 13 studies included incomplete data. Eventually, five papers entered our meta-analysis.

QUALITY ASSESSMENT

Regarding eligibility of articles, we used Jadad or NOS (Newcastle-Ottawa Scale) Checklist to assess the selected papers through the method and other aspects of the study. The supervisor of the study considered any disagreement.

STATISTICAL ANALYSIS

STATA 13.1 software was used for statistical analysis. Heterogeneities were assessed using I-square (I^2) test²⁴. The fixed effects model was used for pooled estimation since there was no heterogeneity between study results²⁵. p -values less than 0.05 were considered statistically significant. This protocol is registered in International Prospective Register of Systematic Reviews (PROSPERO) with identification number CRD42016051663.

RESULTS

By searching databases, 115 articles were obtained, after removing duplicates, 79 articles were entered the screening stage, and finally, five articles were

entered into the meta-analysis (Figure 1). Characteristics of the studies entered into the meta-analysis were presented in Table I. Finally, 8013 patients in the exposed group and 8000 patients in the non-exposed group entered into the survey. In the present survey, the relationship between garlic consumption and gastric cancer mortality was evaluated by meta-analysis of p -values and pooled analysis showed a significant relation ($p=0.007$) between garlic consumption and mortality in gastric cancer patients. In three studies, the number of deaths was reported and pooled estimation indicated that mortality risk of patients with garlic consumption was 0.96 times of other patients (Figure 2) but this relation was not statistically significant. Figure 3 shows that the mortality hazard ratio in gastric cancer with garlic consumption was 46% less than the control group.

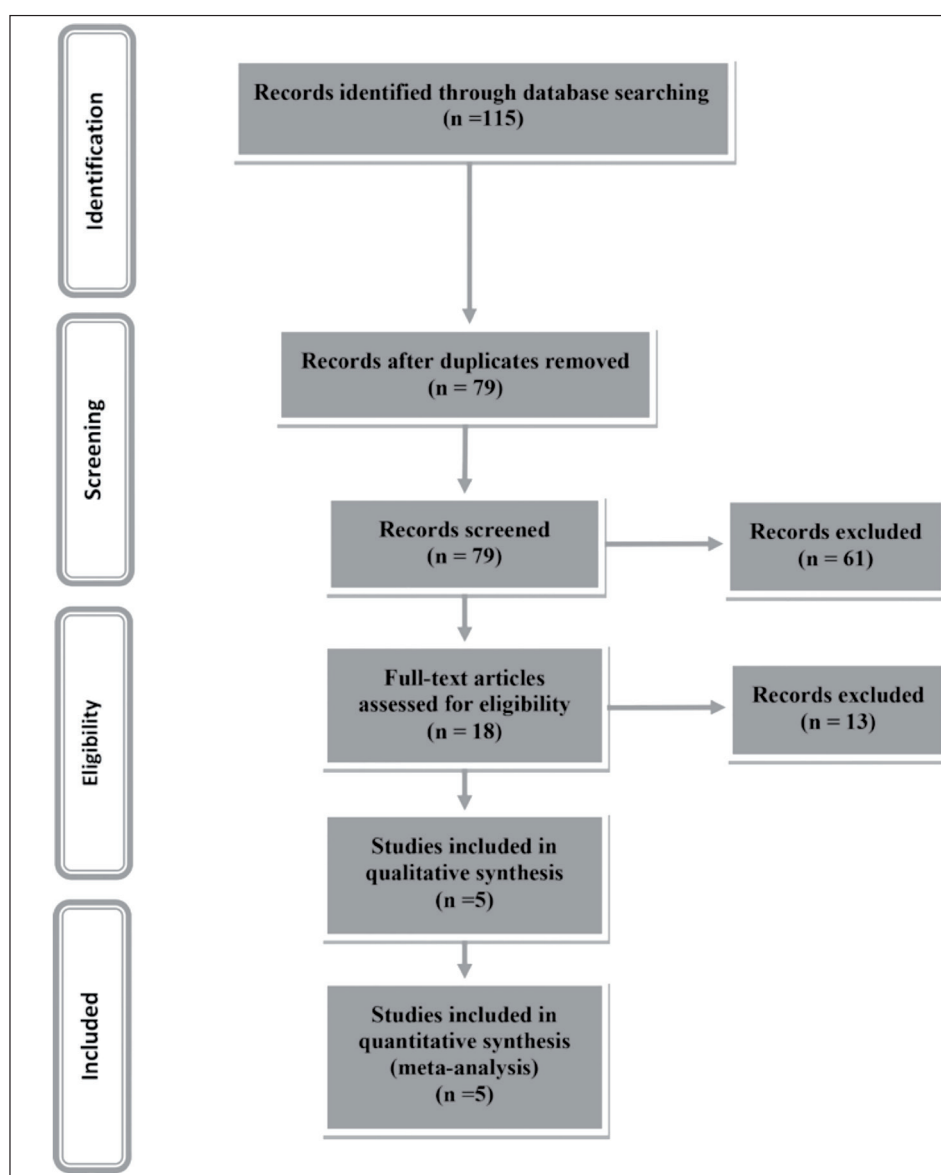


Fig. 1. PRISMA Flowchart for search strategy and study selection.



TABLE 1. Characteristics of the studies that entered the meta-analysis.

Study	Case	Control	Supplement* (mg/day)	Case death	Control death	Total death	p-value	HR (CI)
Takezaki et al ²⁶	425	414	—	—	—	—	0.001	—
You et al ²⁷	1706	1705	800 (+4 mg oil**)	17	14	31	0.719	—
Hao et al ²⁸	2526	2507	200	22	30	52	0.067	0.36 (0.14-0.92)
You et al ²⁹	1678	1687	200 (+2 mg oil**)	12	9	21	0.780	-
Ma et al ³⁰	1678	1687	—	—	—	43	0.170	0.65 (0.35-1.20)

Abbreviation: Ref: Reference, HR: Hazard ratio, CI: Confident Interval, *Garlic extract, **steam-distilled garlic oil.

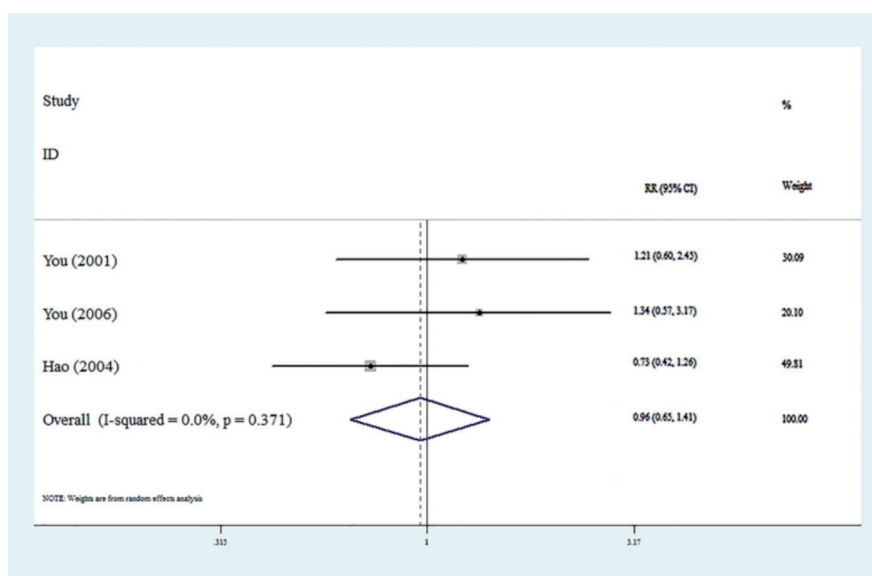


Fig. 2. Forest plot for mortality rate in gastric cancer patients with garlic usage in comparison with control.

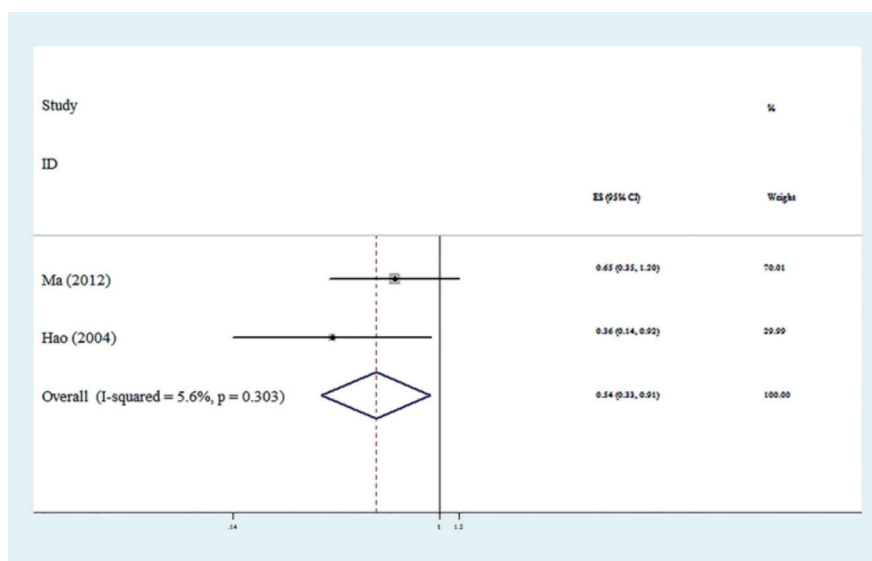


Fig. 3. Forest plot for Hazard ratio of gastric cancer patients with garlic usage in comparison with control.

DISCUSSION

Different investigations studied the probable relationship of gastric cancer risk and *allium* vegetable consumption; nevertheless, our study has investigated the relationship between the mortality of gastric cancer and consumption of garlic as an *allium* vegetable. Our systematic review and meta-analysis showed the reduction of risk of mortality among patients with garlic consumption in comparison to the control group without garlic intake. However, various factors such as type and duration of the study, duration of garlic consumption, dosage of garlic intake, type of garlic supplement, patients' sample size, geographic location of study, etc. can affect the results. For example, according to the mentioned factors, the questionnaire-based study of Takezaki et al²⁶, which performed as a 10-year study in China, suggested that the regular intake of *allium* vegetables like garlic along with other anticancer foods might be associated with a reduction in the mortality rate of GC. In contrast, a 10-year intervention trial in China conducted by You et al^{27,29} indicated that garlic intake had no effect on the progression and regression of GC. In addition, the study of Hao et al²⁸ as a 12-year interventional double-blind trial in China demonstrated that high doses of garlic intake might affect the prevention of GC. However, our meta-analysis result showed the significant relation between gastric cancer and garlic intake, these ranges of differences between studies, which were performed in the approximately same geographical region with nearly identical race show that different listed factors or other unknown factors involved in these diverse outcomes. For example, about dosage of supplements, there is no standard for garlic consumption between studies and there are significant variable definitions for intake dosage. For example³¹, high doses in different studies reported by >1.5 kg/year, >1 time/week, 200 mg/day, etc. and low doses included <1.5 kg/year, <1 times/week, several times/week, etc. Therefore, the need for a certified therapeutic criterion is required. Moreover, different types of garlic such as fresh or processed garlic, garlic oil, garlic extract, and garlic pill were used in the previous studies or not mentioned. Besides, different approaches to cooking such as boiling, frying and even oven temperature of *allium* vegetables can affect the bioavailability and efficacy of their bioactive compounds³². For example, study of Shin et al³³ proved that the concentration of allicin and its anti-inflammatory effects on the fresh garlic was significantly higher than processed garlic extract. Hence, It is questionable whether different types of garlic and consumption modalities can have different effects or not. In addition, the other remarkable limitation is inhibition of *H. Pylori* as the main cause

of gastric cancer³⁴ by the antibacterial effect of garlic supplement³⁵ and it may interfere with this association. Only studies of Pakseresht et al³⁶ and Pourfarzi et al³⁷ from Iran indicated a significant protective role of garlic consumption by providing Risk Ratio estimates adjusted for the presence of *H. Pylori* infection against this confrontation. Therefore, a solution to prevent these overlaps should be taken. Finally, biological mechanisms for reducing the risk of gastric cancer about *allium* vegetables have already been discussed and the anticancer effect of *allium* vegetables seems to be mainly due to the presence of organosulfur compounds^{18,38}. Besides, protective effects of organosulfur compounds against GC proved in the previous preclinical studies²². One of the remarkable strength of our meta-analysis is to provide the new analytical results regarding the role of garlic in gastric cancer prognosis, which not found in the previous systematic reviews. Moreover, the study included by some limitations such as lack of enough comprehensive cohort studies on the prognostic effect of garlic intake on GC, lack of ample evidence about different types of garlic and its intake modalities, and disregard overlaps with other underlying factors, which are important questions for future research.

CONCLUSIONS

Our systematic review and meta-analysis showed that the high consumption of garlic supplements reduces the mortality hazard ratio of gastric cancer. Therefore, according to that, garlic intake is an inexpensive approach and there is no proven side-effects concern related to the high dosage of consumption, it is recommended to being in the daily meal. However, more comprehensive studies required filling the mentioned gaps.

CONFLICT OF INTEREST:

The Authors declare that they have no conflict of interests.

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