Does Garlic Reduce Risk of Colorectal Cancer? A Systematic Review

Suong N. T. Ngo, Desmond B. Williams, Lynne Cobic, and Richard J. Head

Abstract

Colorectal cancer (CRC) is the 3rd leading cause of cancer death in the United States and the 2nd leading cause of cancer death in Australia. Environmental factors play important roles in the multiple-stage process of CRC and nutritional intervention has been identified as playing a major role in its prevention. The aim of this study was to review systematically the scientific evidence from all studies conducted over the last decade that examined effects of garlic on CRC. Levels of evidence were ranked from level I to level V according to study designs and the quality of each study was assessed against a set of quality criteria based on those used by the National Health and Medical Research Council in Australia. One randomized controlled trial (RCT, level II) reported a statistically significant 29% reduction in both size and number of colon adenomas in CRC patients taking aged garlic extract. Five of 8 case control/cohort studies (level III) suggested a protective effect of high intake of raw/cooked garlic and 2 of 8 of these studies suggested a protective effect for distal colon. A published meta-analysis (level III) of 7 of these studies confirmed this inverse association, with a 30% reduction in relative risk. Eleven animal studies (level V) demonstrated a significant anticarcinogenic effect of garlic and/or its active constituents. On balance, there is consistent scientific evidence derived from RCT of animal studies reporting protective effects of garlic on CRC despite great heterogeneity of measures of intakes among human epidemiological studies.

Introduction

Colorectal cancer (CRC) is a main cause of morbidity and mortality in industrial countries. It is the 3rd leading cause of death from cancer for both men and women in the United States (1) and the 2nd leading cause of cancer death in Australia and Canada (2,3). In Australia, CRC is the most common cancer reported to the Australian cancer registries and is a major health problem, with ~12,600 new cases and 4700 deaths each year (4). Approximately 1 in 21 Australians is likely to develop CRC during his/her lifetime and the risk is higher after the age of 40 and increases progressively from 50 y of age. The latest available national figure showed that CRC was responsible for 13% of cancer deaths in 2001, with an estimated 29,058 life-years lost during his/her lifetime and the risk is higher after the age of 40 (4). Approximately 1 in 21 Australians is likely to develop CRC during his/her lifetime and the risk is higher after the age of 40 and increases progressively from 50 y of age. The latest available national figure showed that CRC was responsible for 13% of cancer deaths in 2001, with an estimated 29,058 life-years lost before the age of 75 y (4).

Most CRC are thought to develop from slowly growing benign polyps (4,5). Environmental factors have a great influence on the multiple-stage process that leads from the precursor lesion to cancer (6) and nutritional intervention has been identified as playing a major role in its prevention (7). Vegetables and certain bioactive plant components possess protective effects on the development of CRC, with research interest focusing on garlic in recent years. Garlic (Allium sativum) belongs to the vegetables of the Allium genus that is characterized by a high content in organo-sulfur compounds and flavonoids. Depending on the conditions of its cultivation, garlic may contain at least 33 different organo-sulfur compounds in addition to amino acids, vitamins, and micronutrients. The allyl sulfur constituents in garlic, which comprise ~1% of its dry weight, are responsible for its health benefits (8–17). The major allyl sulfur content in freshly crushed/chopped/cut 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, such as aged garlic extract (AGE), include S-allylcysteine (SAC) and S-allylmercaptopcysteine, which are water soluble and formed by the process of natural aging bioconversion (14).

Garlic has been widely cultivated and used worldwide for its apparent health benefits for thousands of years. Garlic has been considered to increase longevity and physical strength and found to possess numerous medicinal properties, including antimicrobial, antithrombotic, hypolipidemic, antiarthritic, hypoglycemic,
and antitumor effects (13,14,18–35). Recently, much research interest has focused on the pharmacological properties of garlic and its active constituents, particularly with regard to their effects on the prevention of cancer. In addition to the major allyl sulfur contents, other constituents with antioxidant properties and/or anticarcinogenic activity, including flavonoids (particularly kaempferol), selenium, vitamins A and C, arginine, and fructooligosaccharides are also found in garlic. It is likely that these constituents also contribute to the overall health benefits attributed to garlic (1,8–17,35). In general, fresh garlic contains water, carbohydrates, proteins and fiber, fats, and several essential amino acids, minerals, vitamins and micronutrients. The intake of garlic in humans worldwide varied greatly between countries. Overall, the intake ranged from no consumption to 5 cloves/wk (~15 g or 5 servings/wk). One serving was considered equal to 1 clove of garlic, which is ~3 g. Published human studies demonstrating this wide range of garlic intake is summarized and analyzed in the “Results and Discussion.” No symptoms of garlic toxicity were reported in the literature.

Garlic and its allyl sulfur constituents have been reported to exert their protective effects on colonic carcinogenesis in animal and in vitro studies by several mechanisms, including inhibition of carcinogen-induced DNA adduct formation (36), blockage of cell growth, blockage of cell proliferation, and blockage of angiogenesis (18–20,22–30,32,33,37–42), induction of differentiation and/or apoptosis (8,19,22,23,25,27,34,40,41,43–45), enhancement of carcinogen-detoxifying enzymes (27,29,41) and/or suppression of carcinogen-activating enzymes (21,31), inhibition of cyclooxygenase-2 expression (40), scavenging carcinogen-induced free radicals (14), and inhibition of lipid peroxidation (41). Not only are the major sulfur compounds important in the overall protective effects of garlic against cancers but so too are other constituents described previously, including kaempferol, selenium, vitamins A and C, arginine, and fructooligosaccharides (1,9,12–17,35). The aim of this study was to evaluate and review systematically the scientific evidence derived from all types of studies published over the last decade that examined the effects of garlic and/or garlic active constituents on CRC. This article identifies if there are gaps in existing information and provides future directions for research.

**Methods**

**Studies and data sources.** This review evaluated and summarized scientific evidence from randomized controlled trials (RCT; assigned the highest weight), meta-analyses of case control or cohort studies, case control or cohort studies, key epidemiological studies, and animal studies (assigned lowest weight) that compared garlic and/or garlic constituents at any dose or concentration and duration of treatment to a control. We searched the Medline and PubMed databases for studies published in English, from May 1996 to July 2007 that examined effects of garlic, garlic constituents, and/or allium vegetables on CRC. Human trials cited in the primary search studies published any year were also collected and added to the review. The search terms used were: garlic, *Allium sativum*, allium vegetables, allyl sulfides, DAS, DADS, triallyl trisulfide, SAC, colorectal, colonic, rectal, cancer, prevention, chemoprevention, human, animal, RCT, controlled clinical trial, random allocation, clinical trials, case control, and cohort studies. The references from published studies and journal references that were not available electronically were sourced manually.

**Human trials.** For a human trial to be included in this review, study subjects must have had at least 1 baseline endoscopic procedure for the outcome of adenomatous polyps and the final outcomes needed to have been identified by direct visualization by colonoscopy and confirmed pathologically. In all cases, at least 1 of the primary outcomes must have been reported.

**Ranking of outcome measures.** Outcomes were rated according to a hierarchy of outcome measures, adapted and modified from those used by the National Health and Medical Research Council (NHMRC) Australia (46–48). Subject relevant clinical outcomes (primary outcomes) were rated level I; surrogate outcomes (secondary outcomes; intermediate outcomes being predictive of clinical outcomes) were rated level 2; and measurable variables with an indirect connection to the target outcomes were rated level 3 (details of the ranking of outcome measures are summarized in Table 1).

**Levels of evidence.** Levels of evidence were ranked from level I to level V, adapted and modified from those used by the NHMRC (47), which categorizes studies based on study design in accordance with their general capacity to minimize or eliminate bias. Evidence obtained from a systematic review of all relevant RCT was rated level I; evidence obtained from an RCT was rated level II; evidence obtained from a pseudo-RCT was rated level III; evidence obtained from case control/cohort studies or a meta-analysis/systematic review of case control/cohort studies was rated level III-2; and evidence obtained from case series was rated level IV. In addition to the NHMRC method, evidence obtained from animal studies was included and was rated level V, because the review also evaluated scientific evidence derived from animal studies.

**Quality assessment.** The quality of studies was assessed against a set of quality criteria, adapted and modified from those used by the NHMRC (47,48) and the Cochrane Collaboration (49) (details of the quality criteria are summarized in Table 2). Based on the methodology and results

### Table 1: Raking of outcomes measures

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Human studies</th>
<th>Animal studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 (primary outcomes)</td>
<td>Number of subject with</td>
<td>Number of ACF or ACF with ≥4 aberrant crypts or μCAC</td>
</tr>
<tr>
<td>1) Tumor incidence</td>
<td>1) ≥1 adenoma</td>
<td>Induction of: apoptosis, tumor cell proliferation, DNA adduct formation, or carcinogen-metabolizing enzymes and/or inhibition of carcinogen-activating enzymes</td>
</tr>
<tr>
<td>2) Number and size of tumor</td>
<td>2) &gt;1 adenoma</td>
<td></td>
</tr>
<tr>
<td>3) ≥1 adenoma that is ≥1 cm</td>
<td>3) ≥1 adenoma that is ≥1 cm</td>
<td></td>
</tr>
<tr>
<td>4) new diagnosis of CRC</td>
<td>4) new diagnosis of CRC</td>
<td></td>
</tr>
<tr>
<td>5) percent changes in polyp burden</td>
<td>5) percent changes in polyp burden</td>
<td></td>
</tr>
<tr>
<td>Level 2 (secondary outcomes)</td>
<td>Number of subjects that reported at least 1 adverse effect related to the intervention</td>
<td></td>
</tr>
<tr>
<td>1) Tumor incidence</td>
<td>Induction of: apoptosis, tumor cell proliferation, DNA adduct formation, or carcinogen-metabolizing enzymes and/or inhibition of carcinogen-activating enzymes</td>
<td></td>
</tr>
<tr>
<td>2) Number and size of tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) ≥1 adenoma that is ≥1 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4) new diagnosis of CRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5) percent changes in polyp burden</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* βCAC, β-catenin accumulated crypts.
TABLE 2 Quality criteria from which each type of study was assessed

<table>
<thead>
<tr>
<th>Types of study</th>
<th>Quality criteria assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>1) Random generation of the allocation sequence</td>
</tr>
<tr>
<td></td>
<td>2) Concealment of allocation</td>
</tr>
<tr>
<td></td>
<td>3) Double blinding</td>
</tr>
<tr>
<td></td>
<td>4) Follow-up</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>1) Control for confounders</td>
</tr>
<tr>
<td></td>
<td>2) Measurement of exposure</td>
</tr>
<tr>
<td></td>
<td>3) Double blinding</td>
</tr>
<tr>
<td></td>
<td>4) Follow-up</td>
</tr>
<tr>
<td>Case control studies</td>
<td>1) Random matching for case/control</td>
</tr>
<tr>
<td></td>
<td>2) Measurement of exposure</td>
</tr>
<tr>
<td></td>
<td>3) Case definition</td>
</tr>
<tr>
<td></td>
<td>4) Follow-up</td>
</tr>
<tr>
<td>Meta-analysis/systematic reviews</td>
<td>1) Searching strategy</td>
</tr>
<tr>
<td></td>
<td>2) Inclusion criteria</td>
</tr>
<tr>
<td></td>
<td>3) Quality assessment</td>
</tr>
<tr>
<td></td>
<td>4) Method for summarizing</td>
</tr>
<tr>
<td></td>
<td>5) Method for pooling data</td>
</tr>
<tr>
<td></td>
<td>6) Investigation of sources of heterogeneity</td>
</tr>
<tr>
<td>Animal studies</td>
<td>1) Matching for treated or control</td>
</tr>
<tr>
<td></td>
<td>2) Measurement of exposure</td>
</tr>
<tr>
<td></td>
<td>3) Treated/un-treated definition</td>
</tr>
<tr>
<td></td>
<td>4) Follow-up</td>
</tr>
</tbody>
</table>

as they appeared in the publications, each criterion received a grade A if the assessed criterion was adequately conducted. Grades B, C, or D corresponded to whether the assessed criterion was unclear, inadequate, or not conducted, respectively.

**How the qualified studies were compared.** Quality grades were then assigned to the assessed studies in accordance with the Cochrane Handbook (49). Studies were deemed as grade A (low risk of bias) if all quality criteria being assessed received a grade A. Studies were deemed as grade B (moderate risk of bias) or C (high risk of bias) when 1 or more criteria received a grade B or C/D, respectively. We sought clarification from the primary author if the published data provided inadequate information for the review.

Due to great differences in study designs of human dietary intervention trials as well as the diversity of the types of studies collected, no formal statistical analysis was performed.

**Results and Discussion**

**Human studies.** We reviewed a total of 43 studies, of which 10 human and 11 animal studies were identified and deemed as grade A; the remaining were vitro studies. Descriptions of the identified high quality studies published over the last decade that examined the effects of garlic and/or garlic constituents on CRC are available in Supplemental Tables 1 and 2.

Only 1 RCT of CRC incidence (level II evidence) in English was identified from the last 10 y. There were 2 publications on this RCT that examined different types of outcomes (detailed in Table 1); the study published in 2006 reported a significant suppression in both the total size and number of adenomas in CRC patients taking AGE (50) and the study published in 2004 reported a 29% reduction in developing at least 1 new adenoma in these patients, with a reported relative risk of 0.71 (51). These results were based on a relatively small sample of 37 patients with CRC. In the 2004 and 2006 studies, 51 patients were randomized to high or low AGE and given 3 capsules twice per day (2.4 mL or 0.16 mL USP) garlic fluid extract (52); 76% of the treated and 69% of the control group completed the 12-mo trial, with 12 patients withdrawn within 6 mo due to poor follow-up colonoscopies, not following test protocol, or having personal or family issues (50,51).

Five case control (53–57) and 3 cohort studies (58–60) of CRC (level III evidence) were identified. All of the studies were rated as high quality. Overall, 5 of the 8 high quality human studies suggested a protective effect of a high intake of garlic. One published meta-analysis (level III evidence) of 7 of these case control/cohort studies was indentified that confirmed this inverse association, with a reported 30% reduction in CRC relative risk (61). The meta-analysis excluded the largest study that showed no association. One case control study focused on colorectal polyps as opposed to CRC (55). These studies were conducted in Switzerland (53), the United States (54,55,58,59), Argentina (56), China (57), and the Netherlands (60) and measured raw and cooked garlic intake. One cohort study examined garlic supplement (60) and 1 case control study combined raw cooked garlic with onions and peppers into a single exposure category (56). The relative risk estimate, 95% CI, P-value, year of publication, country and number of subjects, garlic categorization, and adjustment for covariates were abstracted from these studies (Supplemental Tables 1 and 2).

The size of the 3 cohort studies ranged from over 3100 participants to ~48,000 participants; 1 cohort study included both male and female populations (60), whereas the other 2 examined either male (59) or female populations (58). Participants for 3 of the 5 case control studies were recruited from hospitals (53,55,57) and the other 2 case control studies included population controls (54,56). Sample sizes of the case control studies ranged from 109 to 698 cases, with a participation rate of ~66–92% for cases and 71–86% for controls. In 1 case control study, the participation rate appeared to be 100% (57). The main reasons for nonparticipation included death before contact (54,56), severe illness (54,56), refusal (53–56), or inability to locate the subject (54,55). With regard to control selection bias, cases were pathologically confirmed by colonoscopy in all case control and cohort studies and were linked with a cancer registration system in 4 of the case control and cohort studies (53,54,58,60). The main inclusion criteria for the comparison (or control) group or cohort included no history of CRC or polyps, no cancer (other than skin cancer), no severe gastrointestinal conditions, or no conditions related long-term modification of diet at baseline (53–56,31–33). In addition, 4 of the case control studies demonstrated a satisfactory participation for cases and controls of >80% and the follow-up rate of the cohort studies was 80 (59) to 95% (59,60).

With respect to control information bias and confounding, all case control and cohort studies utilized some form of FFQ that was previously validated and/or used. The questionnaire collected information on the frequency of usual intake of foods during 1- (55,58–60) 2- (53), 3- (54), or 5-y periods (56) prior to interview. In 6 of the 8 studies, the number of food items ranged from over 125 items to over 280 items and 2 case control studies utilized a FFQ comprising 25 (57) or 79 items (53). In all studies, the type of food items, food categorization, and how food intake was standardized and measured were described adequately. For example, most studies reported the names of food items, the types of measures (such as portion sizes, measuring spoons, and cups being used in the FFQ), and how they were used to facilitate quantification of intake as well as method for calculation of intake, etc. There was considerable variability in the measure of food intake between studies. For example, the highest intake
category reported in 1 study was >14.27 g/wk (56), whereas in another study it was >3 g/wk (58); some did not provide specific quantitative cutoffs (53,57).

The majority of the studies adjusted for several covariates, including age (53,54,56,58–60), sex (53,56,60), history of CRC (54,59,60), total energy intake (53–55,58,59), tobacco (53–55, 58–60), alcohol (53,54,58), BMI (53,55,58), physical activity (53–55,58), education (53,58,60), and race (55). One case control study did not adjust for other factors (57).

Five of 8 of the case control and cohort studies showed an inverse association for the highest intake of raw/cooked garlic and colon and/or rectal cancers compared with no intake. Two case control studies demonstrated a strong protective effect for both the highest and medium intake compared with no intake [OR, 95% CI: 0.32, 0.18–0.57 and 0.51, 0.35–0.74, respectively (53)] or OR, 95% CI: 0.22, 0.10–0.51 and 0.44, 0.19–0.91, respectively, in which garlic, onion, and peppers were incorporated into 1 category (56). One case control study showed a strong inverse association for the highest intake compared with no intake (OR, 95% CI: 0.21, 0.05–0.84) that was based on only 109 cases and 109 controls (57). In addition, 1 case control study reported a significant protective effect for the highest intake on incidence of colorectal polyps (OR, 95% CI: 0.63, 0.42–0.95) (55). Only 1 case control study found weak evidence of an inverse association for men (OR, 95% CI: 0.7, 0.5–1.1) and no association for women; these results were unchanged after adjustments for several covariates (54).

Two of the 3 cohort studies included in this review were large U.S. studies that indicated a strong inverse relationship for the highest intake of garlic compared with no intake and colon cancer [relative risk (RR), 95% CI: 0.65, 0.44–0.97] in which a stratified analysis of the distal colon showed an approximate 48% lower risk of colon cancer observed for the highest intake in comparison with no intake of garlic (58) or RR, 95% CI: 0.63, 0.38–1.65, but this finding is not significant and was limited to the distal colon only (59). Only 1 cohort study, examining garlic supplement, did not find an inverse association; it did, however, detect a nonsignificant slightly lower risk for colon and rectal cancer (RR, 95% CI: 0.93, 0.51–1.71 and 0.77, 0.41–1.46, respectively), which was based on only 443 colon and rectal cases, respectively (60).

Due to great heterogeneity of measures of intake among case control and cohort studies, it is not possible to determine the minimum intake of garlic necessary to exhibit a protective effect. Overall, the case control and cohort studies demonstrated a consistent inverse association between a high garlic intake and CRC.

**Animal studies.** Eleven animal studies of carcinogen-induced colonic tumorigenesis (level V evidence) were identified and included in this review (details are summarized in Supplemental Tables 3–5). These studies reported a significant protective effect of garlic and/or its allyl sulfur constituents. Similar to human studies, most animal studies examined level I outcomes that were subject-relevant clinical outcomes. Overall, most animal studies demonstrated a significant reduction in the incidence and/or growth and multiplicity of carcinogen-induced tumors or a significant reduction in the number of tumor biomarker aberrant crypt foci (ACF), particularly ACF with ≥4 aberrant crypts. One study emphasized effects in the small intestine rather than the colon (39). Although most animal studies mainly utilized ACF as the endpoint, the results obtained in these studies with regard to ACF number/rat were quite contradictory. The findings suggested the potential caveats of emphasis on ACF as the endpoint in animal models of carcinogen-induced colonic carcinogenesis.

Both lipid and water soluble allyl sulfides were effective in suppression of colonic carcinogenesis in a dose- and time-dependent manner. The response to garlic/garlic constituent treatment differed little in animal studies of carcinogen-induced tumorigenesis, whereas the antiproliferative and apoptotic effects appeared to be dependent on the presence of sulfur molecules and whether the agent was lipid or water soluble allyl sulfides. Moreover, colorectal tumors did not respond equally to different garlic allyl sulfur constituents (12). DATS was >10 times more effective than DADS in suppressing colonic tumors (44).

The anticancer properties were detected mainly for AGE (39), garlic suspension (40,41), garlic powder (36), and allyl sulfur constituents SAC (62,63), DADS (42,64), DAS (63,66), and DATS (44), with a less significant effect observed for SAMC. Other anticarcinogenic effects reported by animal studies included: induction of apoptosis by garlic extract (40,41), DAS (66) inhibition of CRC cell proliferation by garlic extract (40,41) and AGE (39), inhibition of carcinogen-induced DNA adduct formation by garlic powder (36), enhancement of carcinogen-metabolizing enzymes by garlic extract (41), inhibition of cyclooxygenase-2 expression by garlic extract (40) and DAS (66), and inhibition of lipid peroxidation by garlic extract (41). The reported minimum amounts of DATS, DADS, SAC, and DAS that were required to bring about the response were 6, 100, 125, and 1000 mg/kg body weight daily, respectively (44, 62–65). The identified animal studies have provided important insight into the mechanisms of CRC protection by garlic and its active allyl sulfur constituents. No significant adverse effects have been reported in any of the identified studies.

In summary, there is substantial and consistent scientific evidence derived from RCT (level II) of animal studies (level V) demonstrating protective effects of AGE, fresh garlic extracts, and active garlic organosulfur constituents against CRC despite great heterogeneity of measures of intakes among human epidemiological studies. The findings suggested that garlic must be considered as part of the entire diet. It is likely that dietary patterns have important influences on the response to garlic. The literature has suggested that a diet high in red meat and fat may increase an individual's risk of getting CRC (67), whereas other micronutrients such as folate; methionine; vitamins B-6, B-12, C, and E; selenium; and lycopene have been found to be protective for CRC (68). Given the small sample size examined by the current RCT, future RCT is warranted to better confirm the protective effect of garlic in CRC.

**Literature Cited**


27. Amagase HSE, Milner JA. Dietary components modify the ability of garlic to suppress 1,2-dimethylbenz(a)anthracene-induced mammary DNA adducts. J Nutr. 1996;126:817–24.


