

Garlic consumption and cancer prevention: meta-analyses of colorectal and stomach cancers¹⁻³

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ABSTRACT

Background: Animal and in vitro studies have provided evidence of an anticarcinogenic effect of active ingredients in garlic.

Objective: The objective was to conduct meta-analyses of the epidemiologic literature on the association between garlic consumption and risk of stomach, colon, head and neck, lung, breast, and prostate cancers.

Design: Meta-analyses were conducted for all cancers mutually and separately for colorectal and stomach cancers in relation to consumption of exclusively raw garlic, cooked garlic, or both (RC garlic). Eighteen studies reported a relative risk estimate for RC garlic consumption and cancer risk.

Results: In the meta-analyses of colorectal and stomach cancer, the reference categories ranged from no consumption to consumption of 3.5 g/wk, whereas the highest categories ranged from any consumption to >28.8 g/wk. The average difference between the highest and lowest categories was 16 g/wk. The random-effects relative risk (RR) estimate of colorectal cancer and RC garlic consumption, excluding garlic supplements, was 0.69 (95% CI: 0.55, 0.89). For stomach cancer, the random-effects RR estimate was 0.53 (95% CI: 0.31, 0.92). The heterogeneity among studies for the latter outcome ($P = 0.0002$) indicates the questionableness of the generalizability of this summary estimate. An indication of publication bias for all cancers combined is evident from a funnel plot of RC garlic consumption and cancer risk and from the results of the Begg and Mazumdar test ($P = 0.049$).

Conclusions: High intake of RC garlic may be associated with a protective effect against stomach and colorectal cancers. Heterogeneity of effect estimates, differences in dose estimation, publication bias, and possible alternative hypotheses (eg, confounding by total vegetable consumption) preclude sole reliance on summary effect estimates. *Am J Clin Nutr* 2000;72:1047-52.

KEY WORDS Garlic, *Allium* vegetables, cancer risk, colorectal cancer, stomach cancer, meta-analysis, epidemiology, prevention

INTRODUCTION

Numerous scientific reports imply that vegetable intake may affect cancer incidence. Epidemiologic studies offer evidence that a high consumption of vegetables reduces the risk of colorectal and stomach cancers (1). In addition, there is some evidence that

the same is true for cancers of the breast, larynx, and prostate (1). On the basis of results of animal and in vitro studies indicating an anticarcinogenic effect of garlic (*Allium sativum*), a review of the epidemiologic literature was conducted and presented elsewhere (2, 3). The review suggested a protective effect of high intakes of garlic against cancers of the stomach, colon and rectum, breast, prostate, and larynx. Since the results of this review were published, 3 additional studies of garlic consumption and cancer reported results supporting this hypothesis (4-6). Motivated by this and the findings of animal experiments, we report results from site-specific meta-analyses of the relation between the consumption of raw garlic, cooked garlic, or both raw and cooked garlic (RC) and the risk of cancer in humans.

METHODS

Epidemiologic studies included in these meta-analyses were identified through a literature search conducted in August 1999. The MEDLINE database (National Library of Medicine, Bethesda, MD) was searched for articles published between 1 January 1966 and 15 August 1999. The reference terms *garlic*, *Allium vegetable*, *vegetable*, *diet*, and *nutrition* in combination with *cancer*, *neoplasm*, and individual cancer subtypes were used as both key words and subject terms. The search was limited to human studies published in English. In addition, journal articles cited in the primary articles were collected and added to the review. From the ≈ 300 studies of vegetable consumption and cancer risk, 22 reported a relative risk (RR) estimate for RC garlic intake and cancer risk. Two of these studies examined the combination of RC garlic and total *Allium* vegetable consumption and 4 studies examined garlic supplements only. The adjusted RR estimate, CI, P value, year of publication, country, number of subjects, and RC garlic categorization and covariates were abstracted from these studies. From each published report, RR estimates and 95% CIs for the

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²Supported by the National Cancer Institute (training grant CA72319-01A1).

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Received August 31, 1999.

Accepted for publication March 8, 2000.

TABLE 1
Garlic consumption and stomach cancer: epidemiologic studies¹

Reference	Country	Subjects	Consumption	OR ²	RR ²
Case-control studies					
You et al (7)	China	564 cases, 1131 controls	0 kg/y	Referent	—
			0.1–1.5 kg/y	0.8 (0.5, 1.2)	—
			>1.5 kg/y	0.7 (0.4, 1.0)	—
Buiatti et al (8)	Italy	640 males, 376 females, 1159 controls	<0.69 servings/wk	Referent	—
			0.70–1.61 servings/wk	0.6 (NA)	—
			1.61–7.15 servings/wk	0.4 (NA)	—
Hansson et al (9)	Sweden	218 males, 120 females, 669 controls	0 servings/mo	Referent	—
Gao et al (6)	China	110 males, 43 females, 234 controls	>0 servings/mo	0.89 (0.64, 1.24)	—
			<1 servings/mo	Referent	—
			1–3 servings/mo	0.40 (0.2, 0.8)	—
			≥4 servings/mo	0.31 (0.2, 0.4)	—
Cohort studies					
Dorant et al (10)	Netherlands	106 males, 33 females, 3123 controls	No supplements	—	Referent
			Garlic supplement only	—	1.27 (0.6, 2.6)
			Other supplements	—	Referent
			Garlic and other supplements	—	1.28 (0.5, 3.7)

¹OR, odds ratio; RR, relative risk; NA, not available.²95% CIs in parentheses.

highest category of RC garlic intake compared with the lowest were extracted. Reference groups consisted primarily of non-consumers of RC garlic. Details of the studies are presented in **Tables 1–4** by cancer site and study design. The individual studies included in the meta-analyses were presented and cri-

tiqued in a previous review (2), except for reports published after 1 August 1998 (4–6).

Publication bias was assessed by using a funnel plot method (25). The log RR estimates are plotted against the inverse of the squared estimated SE of the RR estimate (26). Details of this

TABLE 2
Garlic consumption and colorectal cancer: epidemiologic studies¹

Reference	Country	Subjects	Consumption	OR ²	RR ²
Case-control studies					
Iscovich et al (11) ³	Argentina	62 males, 48 females, 220 neighbor controls	≤66 servings/y	Referent	—
			67–248 servings/y	0.42 (0.19, 0.91)	—
			>248 servings/y	0.22 (0.10, 0.51)	—
Le Marchand et al (12)	United States (Hawaii)	698 males, 1192 total controls	≤0.37 g/d	Referent	—
			0.38–0.99 g/d	0.9 (NA)	—
			1.0–1.8 g/d	0.9 (NA)	—
		>1.8 g/d	0.8 (0.5, 1.1)	—	
		498 females, 1192 total controls	≤0.51 g/d	Referent	—
			0.52–1.29 g/d	1.0 (NA)	—
1.30–2.17 g/d	0.6 (NA)		—		
			>2.18 g/d	0.9 (0.6, 1.4)	—
Hu et al (13)	China	109 females, 109 hospital controls	0 kg/y	Referent	—
			>0 kg/y	0.21 (0.05, 0.84)	—
Levi et al (5)	Switzerland	142 males, 81 females, 491 controls	Low intake	Referent	—
			Medium intake	0.50 (0.3, 0.7)	—
			High intake	0.39 (0.2, 0.7)	—
Cohort studies					
Steinmetz et al (14)	United States (Iowa)	212 females, 35004 controls	0 servings/wk	—	Referent
			0.5 servings/wk	—	1.07 (0.77, 1.50)
			≥1.0 servings/wk	—	0.68 (0.46, 1.02)
Giovannucci et al (15)	United States (Boston)	205 males, 47949 controls (Distal colon)	0	—	Referent
			≥2 servings/wk	—	0.77 (0.51, 1.16)
			0 servings/wk	—	Referent
			≥2 servings/wk	—	0.63 (0.38, 1.65)
Dorant et al (16)	Netherlands	243 males, 200 females, 3123 controls	No supplements	—	Referent
			Exclusively garlic	—	1.36 (0.8, 2.4)
			Other supplements	—	Referent
			Garlic and other supplements	—	0.93 (0.5, 1.7)

¹OR, odds ratio; RR, relative risk; NA, not available.²95% CIs in parentheses.³Garlic combined with onions and peppers.

TABLE 3
Garlic consumption and head and neck cancers: epidemiologic studies¹

Reference	Country	Subjects	Consumption	OR ²
Case-control studies				
Esophageal				
Hu et al (17)	China	170 males, 392 hospital controls	0 kg/y	Referent
			0.1–1.5 kg/y	1.2 (0.6, 2.1)
			0.6–2.0 kg/y	0.6 (0.4, 1.0)
Gao et al (18) ³	China	624 males, 1552 controls	>2.0 kg/y	1.0 (0.6, 1.8)
			Quartile 1	Referent
			Quartile 2	1.1 (NA)
			Quartile 3	1.1 (NA)
Gao et al (6)	China	44 males, 37 females, 234 total controls	Quartile 4	1.1 (NA)
			<1 serving/mo	Referent
			1–3 servings/mo	0.48 (0.2, 1.3)
			≥4 servings/mo	0.30 (0.2, 0.5)
Laryngeal				
Zheng et al (19)	China	177 males, 414 total controls	Tertile 1	Referent
			Tertile 2	0.6 (NA)
			Tertile 3	0.5 (NA)
		24 females, 414 total controls	Low intake	Referent
High intake	0.7 (0.2, 2.1)			
Nasal				
Zheng et al (20) ³	China	39 males, 21 females, 414 controls	Never or rare	Referent
			Month or weekly	1.1 (0.6, 2.1)
			Daily	0.6 (0.3, 1.2)

¹OR, odds ratio; NA, not available.

²95% CIs in parentheses.

³Garlic combined as total *Allium* vegetable consumption.

procedure were described elsewhere (25, 26). In brief, the procedure assumes that large studies are more prone to yield results close to the true value than are smaller studies. Larger studies, with smaller SEs and increased power to detect a true effect, will form the spout of a funnel. Smaller studies with larger variance will tend to disperse, forming the cone. Gaps that appear in this graph are an indication of publication bias. Gaps are hypothesized to be particularly likely among studies with high SEs and implausible point estimates. In addition, two-sided *P* values were obtained for a log-rank test of publication bias, developed by Begg and Mazumdar (27). Results for all cancers are presented in **Figure 1**.

A meta-analysis of multiple groupings of the published epidemiologic studies was performed. The SEs were calculated from the extracted RR estimates and 95% CIs by using the following equation:

$$SE = [\ln(RR_{upper}) - \ln(RR_{lower})]/3.92 \quad (1)$$

However, when the 95% CI was not reported, an estimate of the SE was calculated from an exact *P* value (to ≥2 decimal places) by using the following equation:

$$SE = [\ln(RR)]/z \quad (2)$$

where *z* is the *z* score of the normal distribution for the exact *P* value. In converting RC garlic consumption frequency (ie, the number of times RC garlic was consumed in a given time period) into grams consumed per week, one serving size was considered to equal one clove of garlic, or ≈3 g. Average differences in RC garlic consumption between the highest category of intake and the reference group were computed by assigning a midrange dose to each category and averaging values across all reports.

Fixed- and random-effects estimates were computed by using inverse variance weighting (**Table 5**) (26, 28). Fixed-effects estimates assume that the effect measures in the study populations have a uniform value. Random-effects estimates do not assume that the effect measures are uniform across study populations (26, 28); an additional component of among-study variance is added to each study-specific variance estimate. Tests of homogeneity were conducted for each meta-analysis. The *P* values are presented in Table 5.

Seven meta-analyses were performed. The first aggregated all cancer sites and included data from 20 studies; the studies that examined total *Allium* vegetable consumption were excluded because these reports examined the combination of *Allium* vegetable and RC garlic consumption (18, 20). Two separate RR estimates for males and females from the studies by Le Marchand et al (12) and Zheng et al (19) were used. A second meta-analysis of all cancers was performed, excluding 4 cohort studies of the relation between garlic supplement consumption and cancers of the stomach, colon, lung, and breast. These 4 studies, all published by Dorant et al (10, 16, 23, 24), analyzed one population—the Netherlands follow-up cohort. Site-specific meta-analyses were subsequently conducted on colorectal and stomach cancers. Three separate meta-analyses of the colorectal cancer studies were conducted: one included all 8 of these studies, one included all 8 of these studies except that by Dorant et al (16), and one included all 8 of these studies except those by Dorant et al (16) and Iscovich et al (11). The latter study examined the relation between cancer risk and the combined consumption of RC garlic, peppers, and onions. A similar procedure was used for the studies of stomach cancer. All 5 stomach cancer studies were aggregated for



TABLE 4
Garlic consumption and other sites of cancer: epidemiologic studies¹

Reference	Country	Subjects	Consumption	OR ²	RR ²
Case-control studies					
Prostate					
Key et al (21)	England	328 cases, 328 controls	0 servings/mo	Referent	—
			<1 serving/mo	0.94 (0.51, 1.73)	—
			1–4 servings/mo	0.77 (0.49, 1.20)	—
			≥2 servings/wk	0.64 (0.38, 1.09)	—
Breast					
Levi et al (22)	Switzerland	107 cases, 318 hospital controls	Low intake	Referent	—
			Moderate intake	0.7 (0.4, 1.1)	—
			High intake	0.6 (0.3, 0.9)	—
Challier et al (4) ³	France	345 cases, 345 controls	≤6 servings/wk	Referent	—
			7–10 servings/wk	0.52 (0.3, 0.8)	—
			11–12 servings/wk	0.25 (0.1, 0.6)	—
			13–16 servings/wk	0.40 (0.3, 0.6)	—
			>16 servings/wk	0.30 (0.2, 0.5)	—
Cohort studies					
Lung					
Dorant et al (23)	Netherlands	430 males, 54 females, 3123 controls	No supplements	—	Referent
			Garlic supplements only	—	1.78 (1.1, 2.9)
			Other supplements	—	Referent
			Garlic and other supplements	—	0.93 (0.5, 1.9)
Breast					
Dorant et al (24)	Netherlands	469 cases, 1713 controls	No supplements	—	Referent
			Garlic supplements only	—	1.0 (0.6, 1.6)
			Other supplements	—	Referent
			Garlic and other supplements	—	0.98 (0.6, 1.6)

¹OR, odds ratio; RR, relative risk.

²95% CIs in parentheses.

³Garlic combined with onions.

analysis, and then a separate analysis was made after the study by Dorant et al (10) was excluded.

RESULTS

The funnel plot suggests a deficit of studies with a low number of subjects with results indicating a positive association between RC garlic consumption and cancer risk (Figure 1). This was further evidenced in the log-rank test by Begg and Mazumdar (27) for all studies of RC garlic and cancer risk ($n = 17$; $P = 0.049$).

The results of the meta-analyses are presented in Table 5. The mean (\pm SD) intake of the highest consumers of RC garlic across all published reports was 18.3 ± 14.2 g/wk, or ≈ 6 cloves garlic/wk. In the meta-analyses of colorectal and stomach cancer, the reference categories of RC garlic consumption ranged from no consumption to consumption of 3.5 g/wk (≈ 1 clove), whereas the highest categories of RC garlic intake ranged from any consumption to >28.8 g/wk (≈ 9 – 10 cloves). The difference between the midrange dose of the highest consumption categories and the midrange dose of the reference groups was ≈ 16 g/wk (≈ 5 – 6 cloves). Each meta-analysis, except for the most reduced colorectal model ($n = 6$; 2-sided homogeneity; $P = 0.17$), yielded considerable evidence of heterogeneity ($P < 0.0001$ to 0.02). As a result of the limited number of studies, a meta-regression using the aforementioned extracted variables was not performed.

Given these limitations, the random-effects RR estimate for all sites of cancer represented in the literature, after removal of the 4 garlic-supplement studies, was 0.54 (95% CI: 0.43, 0.67). The random-effects estimate for the reduced colorectal model

($n = 6$) was 0.69 (95% CI: 0.55, 0.89). This suggests that high consumption of RC garlic decreases the risk of colorectal cancer from 10% to nearly 50%, with a point estimate of an approximate 30% reduction. The random-effects RR estimate from the stomach cancer model was 0.53 (95% CI: 0.31, 0.92), ie, the RR of developing stomach cancer was reduced by $\approx 50\%$ (95% CI: 10%, 70%) with a high consumption of RC garlic.

DISCUSSION

The published epidemiologic evidence suggests that protection against stomach and colorectal cancers is conferred by consumption of RC garlic. Because the studies we reviewed were observational, and many did not control for other dietary differences, a review of interventional studies may be required to confirm the effect, especially because garlic supplements did not show a similar association. Although the mean consumption in the highest categories in all the studies was reported, it is unclear what the minimum dose of garlic necessary to elicit a protective effect might be because there was great heterogeneity of frequency categories among the highest categories, and some reports did not provide quantitative cutoffs. Evidence of heterogeneity of RC garlic intake among studies is not evidence against an effect; rather, it suggests that there are appreciable differences among the results beyond those expected from chance and thus that a single summary estimate does not adequately reflect the literature. It can be argued that these studies may be subject to biases and that the sample sizes at the higher exposure levels were too small. Thus, the strongest

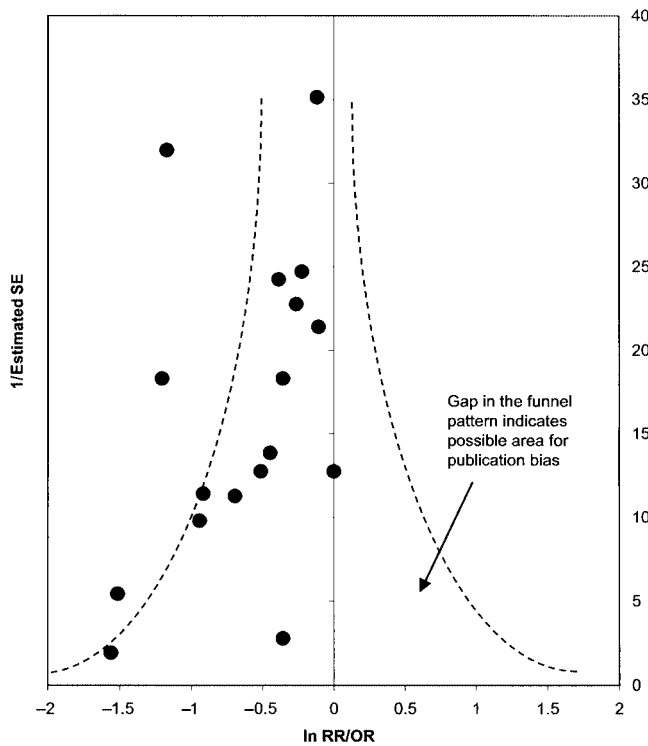


FIGURE 1. Funnel plot indicating publication bias in the studies included in the meta-analyses of the association between garlic consumption and risk of stomach, colorectal, head and neck, lung, breast, and prostate cancers. RR, relative risk; OR, odds ratio.

evidence for a protective effect of RC garlic consumption exists for stomach and colorectal cancers.

Unlike evidence of heterogeneity, evidence of publication bias does detract from the evidence of an effect. Publication bias almost undoubtedly influenced the results, particularly for stomach and colon cancers, for which several studies were available for analysis. The funnel plot indicated that the apparently protective effect found between RC garlic consumption and cancers of the stomach and colon may have been overestimated or, in extreme cases, entirely due to an absence in the published record of reports

with null or positive (RR estimate > 1.0) results. If the funnel plot for all studies, both published and unpublished, had the symmetric shape expected by chance, the summary estimates of effect would be closer to the null value.

In addition to evidence of publication bias, interpretation of these meta-analyses is further limited by other considerations. First, the full cancer model should not be considered representative of all cancers because the literature heavily favors colorectal and stomach cancers; other cancer sites were scant or not represented. The most homogeneous models of colorectal cancer ($n = 6$) and stomach cancer ($n = 4$) consist of only a small number of reports. Furthermore, the stomach cancer model of RC garlic consumption consists of only 4 case-control studies. The RR estimates for both stomach and colorectal cancers never exceeded 1.0 for the highest level of RC garlic consumption compared with the lowest, suggesting either a protective association across all reports or publication bias.

It is possible that residual confounding accounts for some degree of the association because several reports did not control for total vegetable consumption, the known risk factors for these diseases, or both. Promising results for a potentially protective effect of RC garlic consumption against prostate, laryngeal, and breast cancers were observed, although these results were based on only 4 case-control studies. There was divergent evidence to support a relation with esophageal cancer, in which one smaller report showed a protective effect whereas the other 2 showed no association.

On visual inspection of the few studies of garlic supplements, there appeared to be no association with risk of cancer. A positive relation was reported for exclusive users of garlic supplements and risk of lung cancer. This result may be either a spurious association or the outcome of a physiologic or behavioral interaction with known risk factors for lung cancer, such as smoking. Garlic supplement use has been associated with higher levels of education, physical activity, health complaints, and recent dietary change (29). Further research of the association between garlic supplement consumption and cancer risk is necessary before any definitive conclusions can be made (30).

An alternative hypothesis, which may explain the consistent effect seen in meta-analysis, is the protective effect of total vegetable consumption against cancers of the stomach and colon (31). Total vegetable consumption may be positively correlated

TABLE 5
Meta-analysis of relative risk (RR) estimates (95% CIs) by cancer site¹


Model and references	Fixed-effects estimate	Random-effects estimate	P
All cancers, $n = 22$ RRs (4–17, 19, 21–24)	0.65 (0.58, 0.72)	0.63 (0.50, 0.80)	<0.0001
All cancers, excluding the studies by Dorant et al (10, 16, 23, 24), ² $n = 18$ RRs (4–9, 11–15, 17, 19, 21, 22)	0.57 (0.51, 0.64)	0.54 (0.43, 0.67)	<0.0001
Colorectal cancers, $n = 8$ RRs (5, 11–16)	0.72 (0.61, 0.85)	0.66 (0.48, 0.91)	0.003
Colorectal cancers, excluding the study by Dorant et al (16), ² $n = 7$ RRs (5, 11–15)	0.67 (0.56, 0.80)	0.60 (0.44, 0.83)	0.02
Colorectal cancers, excluding the studies by Dorant et al (16) ² and Iscovich et al (11), ³ $n = 6$ RRs (5, 12–15)	0.71 (0.59, 0.86)	0.69 (0.55, 0.89)	0.17
Stomach cancers, $n = 5$ RRs (6–10)	0.57 (0.47, 0.70)	0.61 (0.37, 1.03)	<0.0001
Stomach cancers, excluding the study by Dorant et al (10), ² $n = 4$ RRs (6–9)	0.54 (0.44, 0.66)	0.53 (0.31, 0.92)	0.0002

¹ Mean (\pm SD) consumption for the highest category of raw garlic, cooked garlic, or both (RC) was 18.3 ± 14.2 g/wk for all studies combined. Four studies did not report cutoffs for RC garlic consumption.

² The studies by Dorant et al examined garlic supplements exclusively and cancer incidence.

³ Iscovich et al's study combined garlic, onions, and peppers into a single exposure category.

with RC garlic consumption. In addition, garlic is most often used as a condiment in recipes and dishes such as pasta sauce and is rarely consumed as a single food. Because of the absence of information on total vegetable consumption in the present meta-analyses, it was not controlled for. The random-effects RR estimates presented are adjusted inasmuch as the individual studies controlled for confounding factors. No further adjustment for confounders was made in the meta-analyses. However, except for one study (13) in which the RR estimate was unadjusted, the estimates included in the meta-analysis were the most-adjusted estimates presented in the studies. Typical adjustments were for known cancer confounders such as age, sex, and other factors.

In the present meta-analyses, the inverse association between RC garlic consumption and stomach and colorectal cancers was consistent. In contrast, garlic supplement consumption in one case-control study of prostate cancer and in 4 studies from the Netherlands cohort of colorectal, stomach, lung, and breast cancers did not appear to be associated with cancer risk. Additional studies are required before definitive conclusions can be drawn about the role of RC garlic and garlic supplement consumption in cancer etiology. 

We thank Neal Simonsen for reviewing the manuscript and E Buiatti and L Le Marchand for contributing data additional to those of their published reports.

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