Review Article

Garlic consumption and colorectal cancer risk in man: a systematic review and meta-analysis

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Abstract

Objective: Colorectal cancer shows large incidence variations worldwide that have been attributed to different dietary factors. We conducted a meta-analysis on the relationship between garlic consumption and colorectal cancer risk.
Design: We systematically reviewed publications obtained by searching ISI Web of Knowledge, MEDLINE and EMBASE literature databases. We extracted the risk estimate of the highest and the lowest reported categories of intake from each study and conducted meta-analysis using a random-effects model.
Results: The pooled analysis of all fourteen studies, seven cohort and seven case–control, indicated that garlic consumption was not associated with colorectal cancer risk (OR = 0·93; 95 % CI 0·82, 1·06, $P = 0.281$; $I^2 = 83.6$ %, $P \leq 0.001$). Separate analyses on the basis of cancer sites and sex also revealed no statistically significant effects on cancer risk. However, when separately analysed on the basis of study type, we found that garlic was associated with an approximately 37 % reduction in colorectal cancer risk in the case–control studies (combined risk estimate = 0·63, 95 % CI 0·48, 0·82, $P = 0.001$; $I^2 = 75.6$ %, $P \leq 0.001$).
Conclusions: Our results suggest that consumption of garlic is not associated with a reduced colorectal cancer risk. Further investigations are necessary to clarify the discrepancy between results obtained from different types of epidemiological studies.

Colorectal cancer (CRC) is the third most common cancer worldwide, with an estimated number of new cases and deaths in 2008 of 1·2 million and 608 000 (accounting for 8 % of all cancer deaths), respectively[1]. CRC incidence rates vary markedly worldwide, with rates per 100 000 from 4·1 to 59·1 for males and from 3·6 to 39·5 for females[2]. These large variations have been attributed to different environmental, lifestyle and dietary factors. In particular, diet and nutrition are estimated to explain as much as 50 % of the worldwide incidence of CRC[3].

Among different foods, garlic (*Allium sativum*) has received a particular attention in recent years because of its high content of organosulfur compounds and flavonoids[4]. The allyl sulfur constituents in garlic, which comprise ~ 1 % of its dry weight, seem to be responsible for its chemopreventive effects[5]. In particular, these compounds have been shown to reduce the formation of aberrant crypt foci and to prevent carcinogen-induced colon cancer in different animal models[6]. The mechanisms by which sulfur compounds inhibit cancer cell growth have been the topic of intense research over the last two decades and include: activation of metabolizing enzymes that detoxify carcinogens; reduction of DNA adducts; antioxidant effects; regulation of cell-cycle arrest; induction of apoptosis and differentiation; histone modification; and inhibition of angiogenesis and invasion[7,8]. On the other hand, conclusions from epidemiological research aimed to find an association between garlic consumption and CRC risk are inconsistent or even contradictory[9,10]. In a previous meta-analysis, a risk reduction of 31 % could be observed between CRC and garlic intake (raw and cooked, excluding garlic supplements; RR = 0·69; 95 % CI 0·55, 0·89)[11]. Since then several other studies have been published on this topic with contrasting results. Therefore we conducted a meta-analysis for deriving a more precise estimation of this association.

Materials and methods

Search strategy

Our literature search was aimed at identifying available research studies that examined the effects of garlic on

CRC. Studies included in our meta-analysis were identified by searching, without restrictions, multiple literature databases including ISI Web of Knowledge, MEDLINE and EMBASE, and selecting all articles published up to September 2014. The following strings were used for the search: ('garlic' OR 'allium sativum') AND ('cancer' OR 'neoplastic disease' OR 'neoplasm') AND ('colon' OR 'colorectal' OR 'rectal'). Additionally, we also checked the reference lists of retrieved papers and recent reviews. After removing duplicates in the primary research we identified 439 studies. Although useful to have background information, reviews and meta-analyses were excluded.

Data collection

We systematically reviewed and selected the studies that met all of the following criteria: (i) the study (cohort or case–control) must have had garlic consumption assessed; (ii) it must have provided a risk estimate (hazard ratio, relative risk or odds ratio) for colorectal, colon or rectal cancer incidence as well as its 95 % confidence interval; and (iii) it must have provided information on adjustment for confounding factors. Two investigators reviewed the

eligibility of all studies according to the predetermined selection criteria independently. From the results of the selected studies, we extracted the risk estimate of the highest relative to the lowest intake for the analysis. For the overall estimation the hazard ratio and relative risk were taken to be approximations to the odds ratio, and the meta-analysis was done as if all types of ratio were odds ratios. The combined risk estimate was calculated using a random-effects model in which the effect measures were odds ratios or relative risks. In this analysis data from both females and males, and from colon, rectal and colorectal cancer, as independent populations, were included.

Assessment of study quality

The study quality was assessed by a system based on the Newcastle–Ottawa Scale method[12]. Two investigators (R.F. and M.C.) assessed the quality of each selected study and discrepancies were addressed by a joint re-evaluation of the original article with a third reviewer. The full score was 9 and a total score ≥7 was used to indicate a high-quality study. To avoid selection bias, no study was excluded because of these quality criteria.
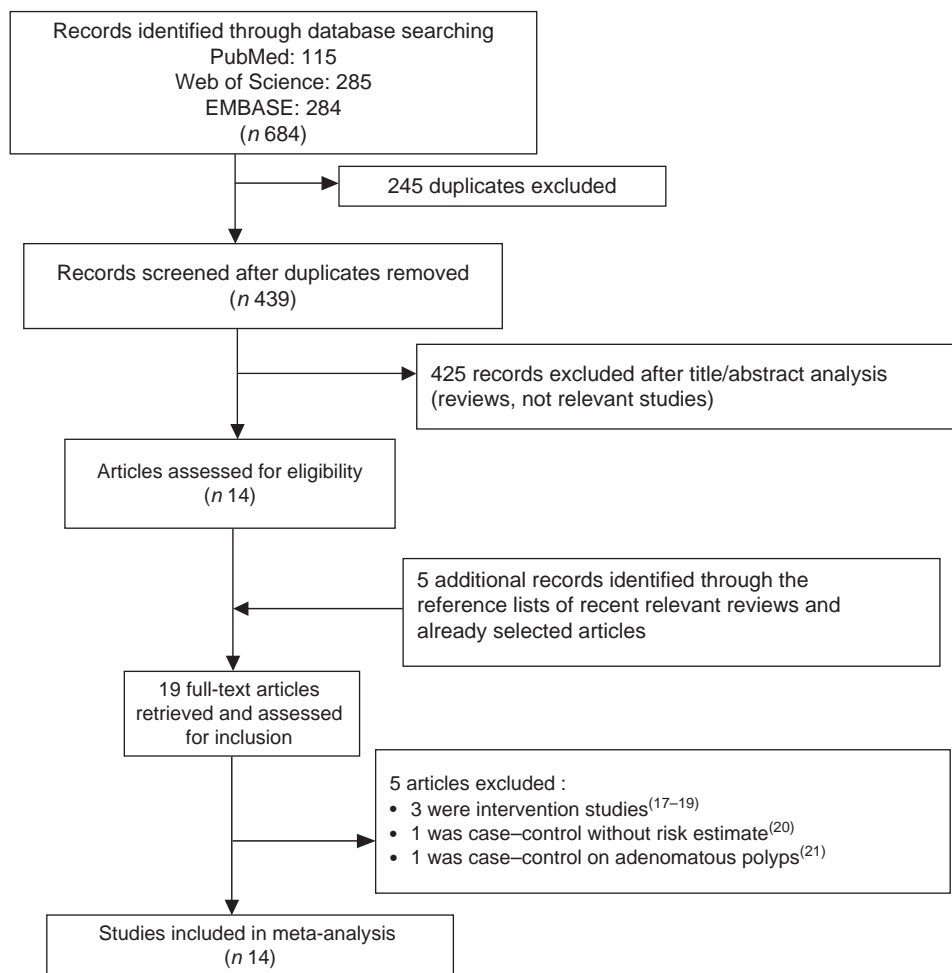

Fig. 1 Flowchart of the study selection process

Table 1 Epidemiological studies on garlic consumption in association with colorectal cancer risk

Reference	Region	Design	Subjects, sex, age	Garlic intake comparisons	HR/RR/OR	95 % CI	Confounding factors adjusted for
Hu et al.[22]	China	Case–control	F (30–65 years) 109 cases/109 controls	0 kg/year >0 kg/year	Rectal: 1.00 0.21	Ref. 0.05, 0.84	Age, sex
Iscovich et al.[23]*	Argentina	Case–control	F+M (mean: 65 years) 110 cases/220 controls	≤66 servings/year 67–248 servings/year >248 servings/year	Colon: 1.00 0.42 0.22	Ref. 0.19, 0.91 0.10, 0.51	Age, sex
Le Marchand et al.[24]	Hawaii	Case–control	F 494 cases/494 controls	≤0.50 g/d 0.51–1.35 1.36–2.20 >2.20 g/d	Colorectal: 1.00 0.7 0.6 0.90	Ref. NA NA 0.60, 1.40	Age, family history, smoking, alcohol, NSP from vegetables
			M 698 cases/698 controls Cases (mean: 66 years) Controls (mean: 64 years)	≤0.40 g/d 0.41–1.10 1.11–1.80 >1.80/d	Colorectal: 1.00 0.9 0.9 0.80	Ref. NA NA 0.50, 1.10	
Levi et al.[25]	Swiss (Vaud)	Case–control	F+M 223 cases/491 controls Cases (mean: 63 years) Controls (mean: 58 years)	Low Medium High	Colorectal: 1.00 0.51 0.32	Ref. 0.35, 0.74 0.18, 0.57	Age, sex, education, smoking, alcohol, BMI, PA, TEI
Galeone et al.[26]	Italy-Swiss	Case–control	F+M 2280 cases/4765 controls Cases (mean: 62 years) Controls (mean: 58 years)	None or low Intermediate High	Colorectal: 1.00 0.88 0.74	Ref. 0.78, 0.98 0.63, 0.86	Age, sex, study centre, education, smoking, alcohol, BMI, PA, TEI
Millen et al.[27]†	USA (multisite)	Case–control	F+M (55–74 years) 1249 cases/11 738 controls	Quintile median: 0.09 serving/d 0.2 serving/d 0.5 serving/d 0.9 serving/d 1.6 servings/d	Colorectal:1.00 0.92 0.94 0.86 0.87	Ref. 0.82, 1.04 0.83, 1.05 0.76, 0.97 0.77, 0.99	Age, sex, race, study centre, education, family history, smoking, alcohol, BMI, PA, use of ibuprofen, aspirin and replacement hormones
Karagianni et al.[28]	Greece (Athens)	Case–control	F+M (30–77 years) 52 cases/56 controls	No Yes	Colorectal: 1.00 0.06	Ref. 0.005, 0.671	Age, sex, smoking, PA, BMI, WC, alcohol, yoghurt, cheese, red meat, fish, fruits, vegetables
Giovannucci et al.[29]	USA	Cohort Follow-up: 6 year	M (40–75 years) 51 529 cohort/251 incident cases	0 serving/week ≥2 servings/week	Colon: 1.00 0.77	Ref. 0.51, 1.16	Age, TEI, previous polyps, family history, smoking, use of aspirin, red meat, methionine, alcohol
Steinmetz et al.[30]	USA (Iowa)	Cohort Follow-up: 5 year	F (55–69 years; mean: 61.7 years) 35 004 cohort/264 incident cases	0 serving/week 0.5 serving/week ≥1 serving/week	Colon: 1.00 1.07 0.68	Ref. 0.77, 1.50 0.46, 1.02	Age, energy intake
Dorant et al.[31]	Netherlands	Cohort Follow-up: 3.3 years (only supplement)	Supplement F+M (55–69 years) 7270 cohort	No supplement Yes supplement	Colon: 1.00 1.36	Ref. 0.79, 2.35	Age, sex, vitamin C, β-carotene, smoking, education, family history, history of chronic intestinal disease or cholecystectomy
			F+M 7672 cohort	No supplement Yes supplement	Rectum: 1.00 1.28	Ref. 0.63, 2.60	
Sellers et al.[32]	USA (Iowa)	Cohort Follow-up: 10 years	F (55–69 years) 22 698 cohort/128 incident cases	0 serving/week ≤1 serving/week >1 serving/week	Colon: 1.0 1.1 1.2	Ref. 0.7, 1.5 0.8, 1.9	Age, TEI, family history

Table 1 Continued

Reference	Region	Design	Subjects, sex, age	Garlic intake comparisons	HR/RR/OR	95 % CI	Confounding factors adjusted for
Satia et al.[33]	USA (Washington)	Cohort Follow-up: 5 year (only supplement)	Supplement F+M (50–76 years) 76 512 cohort/428 incident cases	No supplement Yes supplement	Colorectal: 1·00 1·35	Ref. 1·01, 1·81	Age, sex, education, PA, fruit, vegetable, BMI, NSAID use, sigmoidoscopy
McCullough et al.[34]	USA	Cohort Follow-up: y (also supplement)	F 56 876 cohort/551 incident cases	<1 clove/month 1–3 cloves/month 1 clove/week 2–4 cloves/week k 5–6 cloves/week k ≥1 cloves/d	Colorectal: 1·00 1·18 1·21 1·22 1·41 1·19	Ref. 0·94, 1·49 0·92, 1·59 0·92, 1·60 0·93, 2·15 0·79, 1·79	Age, sex, energy intake, history of endoscopy, BMI, PA, alcohol, smoking, NSAID use, total Ca, fruits, vegetables, red/processed meat, PMH use (F and combined only)
			M 42 824 cohort/579 incident cases	<1 clove/month 1–3 cloves/month 1 clove/week 2–4 cloves/week 5–6 cloves/week ≥1 cloves/d	Colorectal: 1·00 1·08 0·95 0·77 0·74 0·87	Ref. 0·86, 1·35 0·72, 1·26 0·58, 1·02 0·48, 1·13 0·58, 1·32	
			F + M 99 700 cohort/1130 incident cases	<1 clove/month 1–3 cloves/month 1 clove/week 2–4 cloves/week 5–6 cloves/week ≥1 cloves/d	Colorectal: 1·00 1·14 1·08 0·97 0·99 1·03	Ref. 0·97, 1·33 0·89, 1·31 0·79, 1·18 0·73, 1·34 0·77, 1·37	
			Supplement F 51 868 cohort/374 incident cases	Never use Current use	Colorectal: 1·00 1·09	Ref. 0·69, 1·72	
			M 38 053 cohort/390 incident cases	Never use Current use	Colorectal: 1·00 0·94	Ref. 0·57, 1·53	
			F+M 89 921 cohort/753 incident cases	Never use Current use	Colorectal: 1·00 1·03	Ref. 0·74, 1·44	
Meng et al.[35]	USA	Cohort (also supplement)	F (30–55 years) 76 208 cohort/1339 incident cases	<1 clove/month 1–3 cloves/month 1 clove/week 2–4 cloves/week 5–6 cloves/week ≥1 cloves/d	Colorectal: 1·00 1·11 1·07 1·23 1·20 1·21	Ref. 0·94, 1·31 0·89, 1·27 1·04, 1·45 0·96, 1·48 0·94, 1·57	Age, BMI, smoking, family history, history of endoscopy, aspirin use, PA, PMH use; beef, pork and lamb as a main dish, processed meat, alcohol, Ca, folate, vitamin D, TEI
				<1 clove/month 1–3 cloves/month 1 clove/week 2–4 cloves/week 5–6 cloves/week ≥1 cloves/d	Colon: 1·00 1·12 1·05 1·19 1·21 1·23	Ref. 0·93, 1·34 0·86, 1·28 0·98, 1·43 0·95, 1·53 0·92, 1·64	
				<1 clove/month 1–3 cloves/month 1 clove/week	Rectal: 1·00 1·09 1·13	Ref. 0·76, 1·57 0·77, 1·66	

Table 1 *Continued*

Reference	Region	Design	Subjects, sex, age	Garlic intake comparisons	HR/RR/OR	95 % CI	Confounding factors adjusted for
				2–4 cloves/week	1·40	0·98, 2·00	
				5–6 cloves/week	1·14	0·70, 1·86	
				≥1 cloves/d	1·14	0·64, 2·03	
			Males (30–55 years) 45 592 cohort/1029 incident cases	<1 clove/month	Colorectal: 1·00	Ref.	
				1–3 cloves/month	0·99	0·84, 1·16	
				1 clove/week	0·93	0·76, 1·14	
				2–4 cloves/week	0·96	0·80, 1·17	
				5–6 cloves/week	0·90	0·67, 1·20	
				≥1 cloves/d	1·00	0·71, 1·42	
				<1 clove/month	Colon: 1·00	Ref.	
				1–3 cloves/month	0·96	0·80, 1·15	
				1 clove/week	0·90	0·70, 1·13	
				2–4 cloves/week	0·93	0·75, 1·16	
				5–6 cloves/week	0·78	0·55, 1·09	
				≥1 cloves/d	1·09	0·76, 1·58	
				<1 clove/month	Rectal: 1·00	Ref.	
				1–3 cloves/month	1·10	0·77, 1·57	
				1 clove/week	1·10	0·72, 1·70	
				2–4 cloves/week	1·10	0·73, 1·65	
				5–6 cloves/week	1·45	0·82, 2·54	
				≥1 cloves/d	0·60	0·22, 1·66	
			Supplement F 578 incident cases	Yes No	Colorectal: 0·72 Colon: 0·72 Rectal: 0·69	0·48, 1·07 0·46, 1·11 0·28, 1·71	
			M 559 incident cases	Yes No	Colorectal: 1·22 Colon: 1·16 Rectal 1·51	0·83, 1·78 0·75, 1·8 0·71, 3·21	

HR, hazard ratio; RR, relative risk; F, females; M, males; Ref., reference category; NA, not assessed; PA, physical activity; TEI, total energy intake; WC, waist circumference; NSAID, non-steroidal anti-inflammatory drugs; PMH., postmenopausal hormones.
*Garlic, onion and red pepper.
†Garlic and onion.

Statistical examination

Heterogeneity between studies was assessed using the Cochrane Q test and I^2 score. The χ^2-based Cochran's Q statistic and the I^2 statistic were used to quantify evaluated heterogeneity[13]. The I^2 statistic yields results ranging from 0 to 100 % and $I^2 > 50$ % represents substantial heterogeneity[14]. Results of the meta-analysis may be biased if the probability of a study being published is dependent on its results. We used the methods of Begg and Mazumdar[15] and Egger et al.[16] to detect publication bias. Both methods test for funnel plot asymmetry, the former being based on the rank correlation between the effect estimates and their sampling variances, and the latter on a linear regression of a standard normal deviate on its precision. If a potential bias was detected, we further conducted a sensitivity analysis to assess the robustness of combined effect estimates and the possible influence of the bias and to have the bias corrected. We also conducted a sensitivity analysis to investigate the influence of each single study on the overall risk estimate by omitting one study in turn. We considered the funnel plot to be asymmetrical if the intercept of Egger's regression line deviated from zero with a P value of less than 0·10. We should note that this test for asymmetry possesses relatively low power to detect a real publication bias when the total number of studies included in the meta-analysis is small (twenty-five or fewer), which is the case in the current review. The ProMeta Version 2·0 statistical program (Internovi) was used for the analysis. All reported P values are from two-sided statistical tests and differences with $P \leq 0·05$ were considered significant.

Results

The flowchart of the study selection process is shown in Fig. 1. After the analysis of titles and abstracts, we identified fourteen studies on garlic consumption and CRC risk in man. In addition, five studies, identified through the reference lists of recent relevant reviews and already selected articles, were included for the analysis. After the full-text assessment five studies were excluded from the analysis as follows: three were intervention trials that tested the effect of aged garlic extracts on colorectal adenoma occurrence[17–19], one was a case–control study not reporting the risk estimate[20] and one was a case–control study on adenomatous polyps[21] (Fig. 1). Therefore only fourteen studies met the inclusion criteria: seven were case–control[22–28] and seven were cohort studies[29–35] (Table 1). Among the cohort studies two considered garlic supplements only[31,33], while among the other five studies two considered garlic supplements in addition to dietary intake[34,35]. Table 1 summarizes the detailed characteristics of included studies. Three studies reported findings only for females[22,30,32], one only for males[29], eight for females and males together[23,25–28,31,33,34] and three presented findings for males
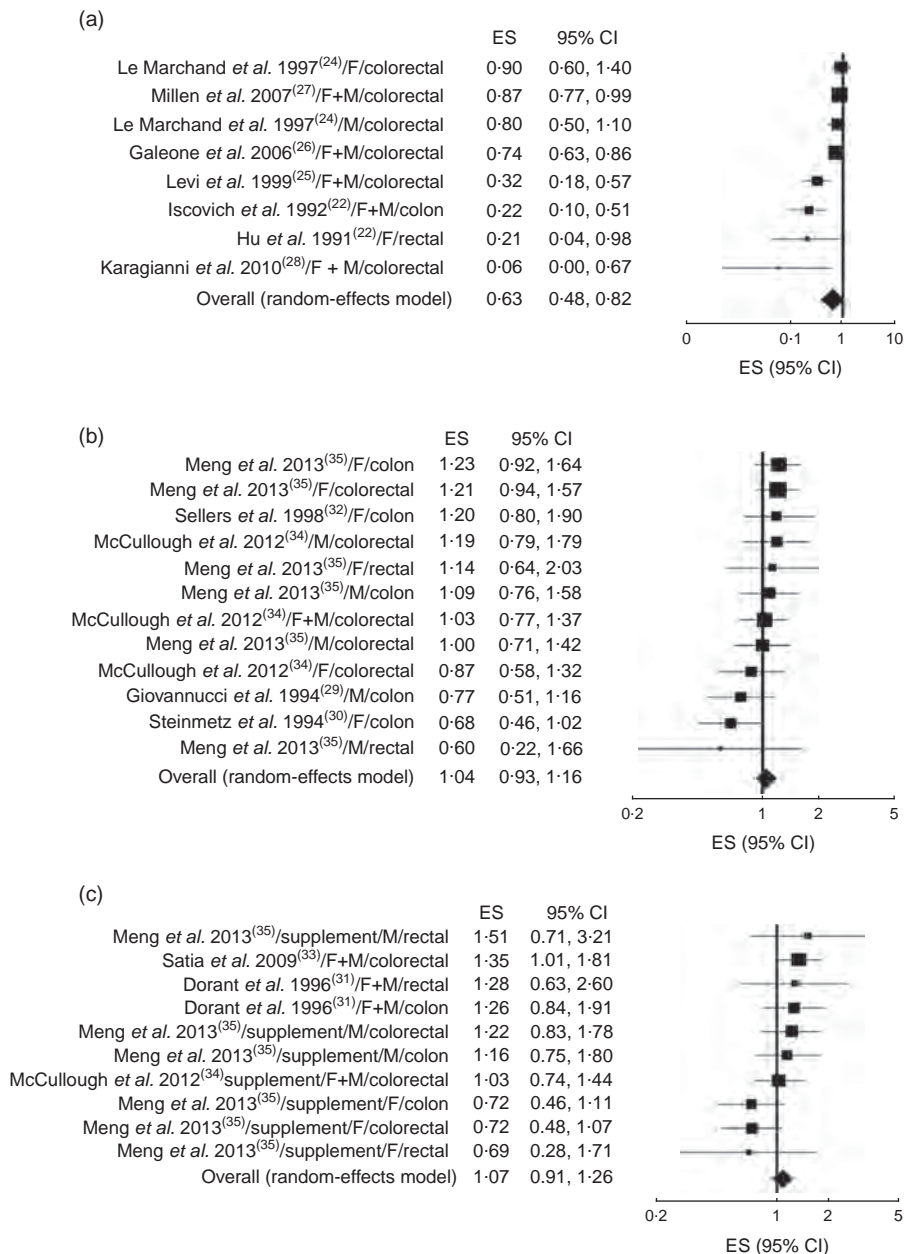
and females separately[24,34,35]. Three studies reported results of risk for rectal cancer[22,31,35], six for colon cancer[23,29–32,35] and eight for CRC[24–28,33–35].

Study-specific quality scores of each study are summarized in Supplemental Table S1 and Supplemental Table S2 for case–control and cohort studies, respectively (see online supplementary material). The ranges of quality score were from 5 to 8 (median: 6) and from 6 to 9 (median: 8) for case–control and cohort studies, respectively. High-quality studies (i.e. those studies that had a score ≥7) included three case–control[26–28] and six cohort[29–34] studies.

The analysis of the fourteen studies pooled together yielded a combined risk estimate of 0·93 (95 % CI 0·82, 1·06; $P = 0·281$) and test of heterogeneity $Q = 176·85$ ($I^2 = 83·6$ %, $P \leq 0·001$). Publication bias was investigated by a funnel plot (Fig. 2). Bias detection revealed a significant effect ($P \leq 0·001$) using the method of Begg and Mazumder[15], while no bias was detected by the Egger test[16] ($P = 0·121$). Sensitivity analyses investigating the influence of each single study on the overall risk estimate by omitting one study in turn suggested that the overall risk estimates were not substantially modified by any single study, with a range from 0·87 (95 % CI 0·73, 1·04) to 0·96 (95 % CI 0·84, 1·08). Of note, the heterogeneity was still observed after omitting each study in turn. Further analyses were performed by stratifying the data on the basis of study type. The forest plots are reported in Fig. 3(a) (case–control studies), Fig. 3(b) (cohort studies) and Fig. 3(c) (supplement studies). The results showed that only in the case–control studies was there a statistically significant reduction (37 %) of cancer risk in association with garlic intake, with a risk estimate of 0·63 (95 % CI 0·48, 0·82; $P = 0·001$; Table 2). Table 2 also reports the results of both heterogeneity and publication bias tests. For the case–control studies only, a high significant heterogeneity was observed while publication bias was significant by the Egger test. A sensitivity analysis excluding Karagianni et al.'s study[24], which caused asymmetry of the funnel plot, yielded a combined risk estimate of 0·65 (95 % CI
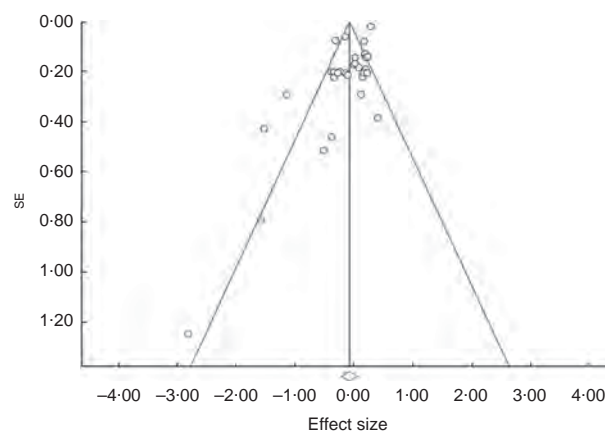
Fig. 2 Funnel plot for the association between garlic consumption and colorectal cancer

(a)

	ES	95% CI
Le Marchand et al. 1997[24]/F/colorectal	0·90	0·60, 1·40
Millen et al. 2007[27]/F+M/colorectal	0·87	0·77, 0·99
Le Marchand et al. 1997[24]/M/colorectal	0·80	0·50, 1·10
Galeone et al. 2006[26]/F+M/colorectal	0·74	0·63, 0·86
Levi et al. 1999[25]/F+M/colorectal	0·32	0·18, 0·57
Iscovich et al. 1992[22]/F+M/colon	0·22	0·10, 0·51
Hu et al. 1991[22]/F/rectal	0·21	0·04, 0·98
Karagianni et al. 2010[28]/F + M/colorectal	0·06	0·00, 0·67
Overall (random-effects model)	0·63	0·48, 0·82

ES (95% CI)

(b)

	ES	95% CI
Meng et al. 2013[35]/F/colon	1·23	0·92, 1·64
Meng et al. 2013[35]/F/colorectal	1·21	0·94, 1·57
Sellers et al. 1998[32]/F/colon	1·20	0·80, 1·90
McCullough et al. 2012[34]/M/colorectal	1·19	0·79, 1·79
Meng et al. 2013[35]/F/rectal	1·14	0·64, 2·03
Meng et al. 2013[35]/M/colon	1·09	0·76, 1·58
McCullough et al. 2012[34]/F+M/colorectal	1·03	0·77, 1·37
Meng et al. 2013[35]/M/colorectal	1·00	0·71, 1·42
McCullough et al. 2012[34]/F/colorectal	0·87	0·58, 1·32
Giovannucci et al. 1994[29]/M/colon	0·77	0·51, 1·16
Steinmetz et al. 1994[30]/F/colon	0·68	0·46, 1·02
Meng et al. 2013[35]/M/rectal	0·60	0·22, 1·66
Overall (random-effects model)	1·04	0·93, 1·16

ES (95% CI)

(c)

	ES	95% CI
Meng et al. 2013[35]/supplement/M/rectal	1·51	0.71, 3·21
Satia et al. 2009[33]/F+M/colorectal	1·35	1.01, 1·81
Dorant et al. 1996[31]/F+M/rectal	1·28	0·63, 2·60
Dorant et al. 1996[31]/F+M/colon	1·26	0·84, 1·91
Meng et al. 2013[35]/supplement/M/colorectal	1·22	0·83, 1·78
Meng et al. 2013[35]/supplement/M/colon	1·16	0·75, 1·80
McCullough et al. 2012[34]supplement/F+M/colorectal	1·03	0·74, 1·44
Meng et al. 2013[35]/supplement/F/colon	0·72	0·46, 1·11
Meng et al. 2013[35]/supplement/F/colorectal	0·72	0·48, 1·07
Meng et al. 2013[35]/supplement/F/rectal	0·69	0·28, 1·71
Overall (random-effects model)	1·07	0·91, 1·26

ES (95% CI)

Fig. 3 Forest plot for the association between garlic consumption and colorectal cancer by study design: (a) case–control, (b) cohort and (c) supplement studies. The study-specific effect size (ES) and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the diamond presents the pooled RR risk and its width represents the pooled 95 % CI (F, females; M, males)

0·51, 0·84; $P \leq 0·01$) with $Q = 24·45$ ($I^2 = 75·5$ %, $P \leq 0·001$), and $P = 0·054$ and $P = 0·176$ for publication bias by the Begg and Egger methods, respectively. We further separately analysed studies according to cancer sites (colon, rectum, colorectal) and sex (female, male, both). No significant effects were observed in all cases (Table 2).

Discussion

The results of the current meta-analysis indicate that, when all selected studies (n 14) were considered, garlic consumption was not associated with CRC risk. A small reduction of risk was observed (7 %) but this effect was not statistically significant. Our results are in contrast with a previous meta-analysis based on seven studies, four case–control[22–25] and three cohort[29–31], which suggested a preventive effect and estimated that high consumption of garlic decreases the risk of CRC by 30 %[11]. In comparison with the previous meta-analysis, our updated search identified and included seven more studies[26–28,32–35] which may be responsible for these discrepancies. In addition, our analysis included the estimated risks associated with the use of garlic supplements which were excluded in the previous

Table 2 Results of stratified analysis on the basis of study type, cancer site and sex

	Combined risk estimate			Test of heterogeneity			Publication bias		References
	Value	95 % CI	P	Q	I² (%)	P	P (Egger test)	P (Begg test)	
Study type									
Case–control (n 7)	0.63	0.48, 0.82	0.001	28.68	75.59	0.0001	0.020	0.138	(22–28)
Cohort (n 5)	1.04	0.93, 1.16	0.538	11.98	8.16	0.365	0.117	0.273	(29,30,32,34,35)
Supplement (n 4)	1.07	0.91, 1.26	0.417	12.47	27.82	0.188	0.634	0.655	(31,33–35)
Cancer site									
Colon (n 6)	0.93	0.74, 1.16	0.515	27.72	71.14	0.001	0.026	0.022	(23,29–32,35)
Rectal (n 3)	1.00	0.69, 1.45	0.989	8.53	41.37	0.129	0.061	0.015	(22,31,35)
Colorectal (n 8)	0.91	0.76, 1.10	0.346	134.64	89.60	0.0001	0.004	0.299	(24–28,33–35)
Sex									
F (n 6)	0.94	0.79, 1.12	0.510	22.19	54.94	0.014	0.005	0.102	(3,22,24,30,32,34)
M (n 4)	1.02	0.89, 1.18	0.766	7.22	0.00	0.513	0.848	0.835	(24,29,34,35)
F+M (n 8)	0.85	0.66, 1.10	0.213	133.95	93.28	0.0001	0.020	0.655	(23,25–28,31,33,34)

F, females; M, males.

meta-analysis[11]. Stratification of the sample on the basis of cancer sites (colon, rectal and colorectal) and sex (female, male and both) also revealed no statistically significant effects on CRC risk. However, when separately analysed on the basis of study type, we found that garlic was associated with a significant reduction (37 %) of CRC risk in the case–control studies while no effects were observed for both cohort and supplement studies. This discrepancy between the case–control and cohort studies may be due to several reasons. Case–control studies have several weaknesses and critical points, which can lead to incorrect conclusions. They are particularly susceptible to recall and selection bias which may produce misclassification of exposure between case and control groups. Moreover, the control group may not be representative of the general population as a consequence of various degrees of selection bias among healthy subjects[36]. In addition, some case–control studies included in the current meta-analysis did not adjust for important confounding factors such as red meat, energy intake, alcohol and others that have been consistently associated with CRC risk[37]. Therefore, as discussed above, findings derived from retrospective studies should be interpreted with caution while cohort studies certainly have a greater degree of reliability. However, it should be noted that six cohort studies out of seven were performed in the USA, so suggesting that geographical differences may exist. Similarly to cohort studies, also the results on supplements suggest that use of garlic supplements was not able to prevent CRC. Our results are in agreement with a recent meta-analysis, published during the preparation of this manuscript, investigating the association between high intake of allium vegetables and CRC risk[38]. In that study, the stratified analysis showed a not statistically significant increase of CRC risk in association with garlic intake in cohort studies (OR = 1·11; 95 % CI 0·95, 1·29)[38]. In addition, the use of garlic supplements was associated with a significant increase of CRC risk (OR = 1·18; 95 % CI 1·02, 1·36)[38]. The small difference with our data may be due to the inclusion in our analysis of two studies[29,30] which were excluded in the above reported meta-analysis[38]. Moreover, in the analysis on supplements we used a random-effects model and excluded data from past use of garlic supplements[34].

Recently, two meta-analyses have been published showing the effects of garlic intake on gastric[39] and prostate cancer risk[40]. Similarly to our results, a preventive effect of garlic on gastric cancer was observed in three hospital-based case–control studies (OR = 0·57; 95 % CI 0·34, 0·80) and in eight population-based case–control studies (OR = 0·52; 95 % CI 0·37, 0·67), while one cohort study showed an increased risk (OR = 1·28; 95 % CI 0·45, 3·66)[39]. Furthermore, the results obtained on prostate cancer were similar to our results in showing that meta-analysis from the case–control studies suggested a significant reduction in risk (OR = 0·77; 95 % CI 0·64, 0·91) while the results from the cohort studies were null (OR = 0·96; 95 % CI 0·89, 1·05)[40]. Several mechanisms have been suggested to participate in

the potential anticancer effects of garlic and its components. Garlic is rich in organosulfur compounds and flavonoids, which have been reported to exert chemopreventive effects in animal and *in vitro* studies by different mechanisms including modulation of carcinogen-metabolizing enzymes, cell-cycle arrest, induction of apoptotic cell death and/or differentiation, suppression of oncogenic signal transduction pathways, and inhibition of neoangiogenesis[8,41]. It should be noted that all of these effects have been evidenced at high doses of compounds which may be not easily reached with the normal human diet. This is particularly evident for garlic, which is generally used in low amounts.

Conclusion

The present meta-analysis provides evidence that consumption of garlic is not associated with a reduced CRC risk. The preventive effect suggested by the case–control studies may be due to potential confounding factors and exposure misclassification. Further studies will be needed to clarify these discrepancies; in particular, cohort studies should be carried out in the continents of Asia and Europe to confirm the US findings.

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Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1368980015001263

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