Research Article

Cancer Prevention Research

Raw Garlic Consumption as a Protective Factor for Lung Cancer, a Population-Based Case–Control Study in a Chinese Population

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Abstract

Protective effect of garlic on the development of cancer has been reported in the *in vitro and in vivo* experimental studies; however, few human epidemiologic studies have evaluated the relationship. A population-based case–control study has been conducted in a Chinese population from 2003 to 2010, with the aim to explore the association between raw garlic consumption and lung cancer. Epidemiologic data were collected by face-to-face interviews using a standard questionnaire among 1,424 lung cancer cases and 4,543 healthy controls. Unconditional logistic regression was used to estimate adjusted ORs and their 95% confidence intervals (CI), and to evaluate ratio of ORs (ROR) for multiplicative interactions between raw garlic consumption and other risk factors. After adjusting for potential confounding factors, raw garlic consumption of 2 times or more per week is inversely associated with lung cancer (OR = 0.56; 95% CI, 0.44–0.72) with a monotonic dose–response relationship ($P_{\text{trend}} <$ 0.001). Furthermore, strong interactions at either additive and/or multiplicative scales were observed between raw garlic consumption and tobacco smoking [synergy index (SI) = 0.70; 95% CI, 0.57–0.85; and ROR = 0.78; 95% CI, 0.67–0.90], as well as high-temperature cooking oil fume (ROR = 0.77; 95% CI, 0.59–1.00). In conclusion, protective association between intake of raw garlic and lung cancer has been observed with a dose–response pattern, suggesting that garlic may potentially serve as a chemopreventive agent for lung cancer. Effective components in garlic in lung cancer chemoprevention warrant further in-depth investigation. *Cancer Prev Res; 6(7); 711–8. ©2013 AACR.*

Introduction

Lung cancer is one of the most common causes of cancer death, with 1.4 million deaths (18.2% of the total) in 2008 globally. The world age-standardized mortality rate (ASR) of lung cancer was 19.3 per 100,000 in 2008 (1, 2). In China, lung cancer is one of the leading causes of cancer death, with the ASR of 20.4 per 100,000 during 1990–1992 and 27.7 per 100,000 in 2008 (3, 4). In Jiangsu province, the ASR of lung cancer morality was 24.3 per 100,000 in early 1990s and has become the first leading cause of cancer death since 2010 with the ASR of 26.1 per 100,000 (5, 6).

Tobacco smoke contains well-established group I carcinogens for lung cancer development by numerous epidemiologic studies and with extensive basic scientific research (7). Specific lung carcinogens defined by International Agency for Research on Cancer include environmental tobacco smoke, occupational exposure such as asbestos, crystalline silica and ionizing radiation, air pollution, coal-related pollution, and indoor emissions from household combustion (8). Frying foods and emissions from high-temperature cooking oil were suggested as risk factors for lung cancer by limited evidence from case–control and *in vitro* studies, particularly among Chinese women (9, 10). Although few protective factors have been identified for lung cancer, a meta-analysis based on limited number of case–control and cohort studies reported that diets high in fruit and vegetables are possibly associated with a reduced risk of lung cancer (11, 12).

Garlic (*Allium sativum*) is a bulbous plant with a strong taste and smell. It is widely consumed as a popular spice added to many edible preparations. The first documented application of garlic in traditional Chinese medicine could be traced back to 2000 BCE, when it was believed to

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possess miraculous properties for curing poisoning. Garlic was recorded in Chinese Herbal Medicine Materia Medica (13–15). When bulb breaks up into separate cloves and its membrane disrupts, there are many organosulfur compounds (OSC) in the volatile oil, including allicin, diallyl sulfide, diallyl disulfide, and diallyl trisulfide (16). Many of the beneficial effects of garlic are attributed to high levels of OSCs (17, 18). The volatile oil with effective OSCs is largely excreted via the lungs, which might be supportive for the hypothesis of the protective effects of garlic for lung cancer. Both *in vitro* and *in vivo* experimental studies have suggested a protective effect by garlic and its compounds for cancer reduction in a variety of sites including lung (19–25). However, very few epidemiologic studies have been conducted to evaluate the relationship between garlic consumption and lung cancer (26–30). On the basis of data collected from a population-based case–control study with large sample size conducted in 2 counties of Jiangsu Province, China (31), we investigated the association of raw garlic consumption with lung cancer, as well as the potential effect modification of relationship between raw garlic consumption and other major risk factors on the development of lung cancer.

Materials and Methods

Population-based tumor registries at county level have been gradually established in Jiangsu Province, Southeast of China since the late 1990s. Among over a dozen of counties with tumor registry, Dafeng and Ganyu counties are considered to have high-quality cancer registry data (32). Both Dafeng and Ganyu counties are coastal rural areas in northern Jiangsu and less economically developed. Populations of Dafeng and Ganyu are approximately 0.7 million and 1.1 million, respectively. Data from 1996 to 2002 showed an average lung cancer mortality of 20.5 per 100,000 for both counties, albeit an insignificant difference between 2 counties (33).

Subjects

This population-based case-control study was conducted from 2003 to 2010 in both Dafeng and Ganyu counties in Jiangsu Province, China. Eligible cases were patients with lung cancer, aged 18 years or older, newly diagnosed with primary lung cancer within 12 months, and have lived as local residents for at least 5 years before face-to-face interviews. Cases were identified from population-based tumor registries of both counties, managed by Centers for Disease Control and Prevention (CDC). Controls were randomly selected from a list of residents from country-specific demographic databases, individually matched with cases for gender and age (±5 years). Individuals with a history of any cancer were excluded. The original plan was to recruit 600 pairs of cases and controls for each county. As parallel case–control studies have been conducted for other cancer sites including cancers of esophagus, stomach, and liver in the same countries, we included controls for all 4 cancer sites in the present analysis to increase statistical power. From 2003 to 2010, 1,424 cases (625 in Dafeng and 799 in Ganyu) and 4,543 controls (2,533 in Dafeng and 2,010 in Ganyu) were recruited for this study. Most of our subjects were recruited from 2003 to 2007 and response rates were 39.5% and 56.8% of eligible cases as well as 87% and 85% of eligible controls in Dafeng and Ganyu, respectively.

Data collection

This study was approved by the Institutional Review Board of Jiangsu Provincial Health Department. Written informed consent was obtained from each of the subjects. Epidemiologic data were collected through face-to-face interviews using a standardized questionnaire including putative risk or protective factors for lung cancer. The questionnaire has been field tested in an early study (34). The interviews of cases took place as soon as they were reported and registered in the county's tumor registry system, and population controls were interviewed twice a year by our interviewers. All interviewers were trained and refreshed on an annual basis. Quarterly quality assurance of questionnaire indicated an overall accuracy of 96.19% for cases and 97.12% for controls based on 10% randomly selected sample of completed questionnaires.

The epidemiologic questionnaire contains information such as basic demographic and social economic status, weekly raw garlic consumption (never, <2 times/week or ≥2 times/week) and quantity (grams/week) of raw garlic intake, tobacco smoking (age starting smoking, years of smoking, number of cigarettes smoked daily, years of quitting), environmental tobacco smoking, other environmental exposures to possible pollution from factories close to their households (factory nearby), indoor air pollution from cooking (kitchen ventilation and oil temperature while cooking), dietary history obtained using a modified version of a validated food frequency questionnaire in Han population (35, 36), family history of lung cancer, or any other cancers and physical activity as well.

Statistical analysis

Data were entered using Epidata 3.0 (EpiData Association), cleaned, and analyzed using SAS v9.2 package (SAS Institute Inc.,). Missing values, less than 10% for all variables, were imputed with the county and gender-specific median value of controls of the specific variable. Sensitivity analyses were performed to compare results between complete case analysis when missing data were excluded and an analysis when missing data are imputed. If the point estimates are equivalent, we present results from imputed data for the specific variable, otherwise, we present results from complete case analyses. χ^2 and Student *t* tests were used to compare the distribution of potential risk and protective factors between cases and controls. Unconditional logistic regression was used to estimate ORs and their corresponding 95% confidence intervals (CI) for both univariate and multivariate analyses. Dummy variables were used in a logistic regression model to estimate the OR for each exposure category. Trend tests were conducted by assigning scores to ordinal levels of exposure and treated the variable as a continuous variable in the logistic regression model. The main association between raw garlic consumption and lung cancer was evaluated, and the potential multiplicative and additive interactions were assessed between raw garlic consumption and other lung cancer risk factors. Multiplicative interaction was evaluated by including main effect variables and their product terms in a logistic regression model. In the additive interaction analysis, preventive factors were recoded in such a way that the stratum with the lowest risk becomes the reference category when both factors were considered jointly (37). We calculated the 3 measures of additive interaction: relative excess risk due to interaction (RERI), attributable proportion due to interaction, and synergy index (SI) and their 95% CIs (38–40). If 95% CIs of the RERI and attributable proportion include 0 and that of SI includes 1, they are interpreted as no obvious additive interaction. Because there was no significant difference in the association between raw garlic consumption and lung cancer between the 2 counties, data from 2 counties were combined to increase the statistical power.

On the basis of prior knowledge and confounding assessment, we adjusted for potential confounding factors including: age (continuous), gender (male = 1, female = 0), education level (illiteracy = 1, primary = 2, middle = 3, high = 4, college = 5), income (Yuan/year) 10 years ago (continuous), body mass index (BMI; continuous), family history of lung cancer (yes = 1, no = 0), pack-year of smoking (continuous), ethanol consumption (mL/week, continuous), and study area (Dafeng = 1, Ganyu = 2).

Results

The demographic information and socioeconomics status of cases and controls are shown in Table 1. No statistically significant differences were observed between cases and controls on the distribution of education level and income 10 years ago, except gender, mean age, and BMI.

The associations between risk or protective factors and lung cancer (ORs and 95% CIs) are presented in Table 2. Tobacco smoking was confirmed as a strong risk factor for lung cancer with adjusted ORs of 2.54 (95% CI, 2.17–2.99) for ever smoking. A strong dose–response pattern was observed between pack-years of tobacco smoking and lung cancer ($P_{\text{trend}} < 0.0001$). Environmental exposure to possible pollution from factories nearby (adjusted OR = 1.55; 95% CI, 1.28–1.89), indoor exposure from high-temperature cooking oil (adjusted OR = 1.26; 95% CI, 1.10–1.43), frequently eating frying foods (adjusted OR = 1.32; 95% CI, 1.15–1.52), and a family history of lung cancer (adjusted OR = 1.98; 95% CI, 1.42–2.74) were positively associated with lung cancer. Inverse associations were observed between lung cancer risk and green tea drinking (adjusted OR = 0.85; 95% CI, 0.73–1.00) and physical exercise 10 years ago (adjusted OR = 0.82, 95% CI = 0.70–0.96).

Table 3 presents the overall association between lung cancer and raw garlic consumption as well as stratified associations by potential confounding factors. After adjusting for potential confounding factors, raw garlic consumption frequency was inversely associated with lung cancer.

Table 1. Demographic information and socioeconomic status of cases and controls

Variables	Case (%; *N* = 1,424)	Control (%; *N* = 4,543)	P^a
Study area			
Dafeng	625 (43.9)	2,533 (55.8)	
Ganyu	799 (56.1)	2,010 (44.2)	
Gender			
Male	995 (69.9)	3,415 (75.2)	
Female	429 (30.1)	1,128 (24.8)	<0.001
Age, y			
Mean (SD)	63.3 (11.1)	64.0 (11.3)	0.037
<50	166 (11.7)	499 (11.0)	
50-	328 (23.0)	989 (21.8)	
60-	468 (32.9)	1,440 (31.7)	
70-	387 (27.2)	1,309 (28.8)	
≥80	75 (5.3)	306 (6.7)	0.173
Education level			
Illiteracy	706 (49.6)	2,309 (50.8)	
Primary	466 (32.7)	1,393 (30.7)	
Middle	197 (13.8)	644 (14.2)	
High	44 (3.1)	174 (3.8)	
College	11 (0.8)	23 (0.5)	0.300
Income 10 years ago (Yuan/year)			
Mean (SD)	2,260 (2170)	2,220 (2481)	0.565
<1,000	284 (19.9)	959 (21.1)	
1,000-	266 (18.7)	843 (18.6)	
1,500-	380 (26.7)	1,234 (27.2)	
≥2500	494 (34.7)	1,507 (33.2)	0.670
BMI[b]			
Mean (SD)	22.2 (4.3)	22.8 (3.6)	<0.001
<18.5	204 (14.3)	307 (6.8)	
18.5–23.9	862 (60.5)	2,881 (63.4)	
24.0–27.9	285 (20.0)	1,103 (24.3)	
≥28.0	73 (5.1)	252 (5.5)	<0.001

[a]On the basis of χ^2 testing; *t* testing for the mean.
[b]Chinese recommend standard was used for the cutoff points of overweight and obesity: low weight (BMI < 18.5), overweight (BMI ≥ 24.0 and BMI < 28.0), obesity (BMI ≥ 28.0).

OR for eating raw garlic less than 2 times per week and 2 times or more per week was 0.92 (95% CI, 0.79–1.08) and 0.56 (95% CI, 0.44–0.72), respectively, compared with individuals who never ate raw garlic. A monotonic dose–response relationship was also observed ($P_{\text{trend}} < 0.001$). Similar inverse associations between raw garlic consumption and lung cancer risk were observed when stratified by study area, alcohol drinking status, factory nearby, high-temperature cooking oil, frying foods, and poor ventilation in kitchen. A significant inverse association between lung cancer and raw garlic consumption was found among smokers but only a borderline association was observed among never smokers (adjusted OR = 0.67; 95% CI, 0.43–1.05).

Table 2. The distribution of major factors and their associations with lung cancer risk

Variables	Case (%; $N = 1{,}424$)	Control (%; $N = 4{,}543$)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Ever smoking				
No	394 (27.7)	1,860 (40.9)	1.00	1.00
Yes	1,030 (72.3)	2,683 (59.1)	1.81 (1.59–2.07)	2.54 (2.17–2.99)
Pack-years of smoking				
Never smoker	394 (27.7)	1,860 (40.9)	1.00	1.00
<30 y	262 (18.4)	1,088 (23.9)	1.14 (0.96–1.35)	1.60 (1.32–1.94)
≥30 y	768 (53.9)	1,595 (35.1)	2.27 (1.98–2.61)	3.68 (3.08–4.40)
P_{trend}			<0.001	<0.001
Alcohol drinking status				
Never or seldom	837(58.8)	2,782 (61.2)	1.00	1.00
Often	587(41.2)	1,761 (38.8)	1.11 (0.98–1.25)	1.04 (0.90–1.19)
Factory nearby				
No	1 216 (86.7)	4,021 (89.9)	1.00	1.00
Yes	186 (13.3)	450 (10.1)	1.37 (1.14–1.64)	1.55 (1.28–1.89)
High-temperature cooking oil				
No	911 (64.0)	3,194 (70.3)	1.00	1.00
Yes	513 (36.0)	1,349 (29.7)	1.33 (1.18–1.51)	1.26 (1.10–1.43)
Consumption of fried food				
No	651 (45.7)	2,539 (55.9)	1.00	1.00
Yes	773 (54.3)	2,004 (44.1)	1.50 (1.34–1.70)	1.32 (1.15–1.52)
Poor ventilation in kitchen				
No	558 (39.2)	1,944 (42.8)	1.00	1.00
Yes	866 (60.8)	2,599 (57.2)	1.16 (1.03–1.31)	1.12 (0.98–1.28)
Family history of lung cancer				
No	1,356 (95.2)	4,433 (97.6)	1.00	1.00
Yes	68 (4.8)	110 (2.4)	2.02 (1.49–2.75)	1.98 (1.42–2.74)
Green tea drinking				
No	952 (71.2)	3,028 (71.9)	1.00	1.00
Yes	386 (28.8)	1,186 (28.1)	1.04 (0.90–1.19)	0.85 (0.73–1.00)
Exercise ten years ago				
No	1,111 (78.0)	3,543 (78.0)	1.00	1.00
Yes	313 (22.0)	1,000 (22.0)	1.00 (0.87–1.15)	0.82 (0.70–0.96)

[a]Adjusted on age (continuous), gender (male = 1, female = 0), education level (illiteracy = 1, primary = 2, middle = 3, high = 4, college = 5), income (Yuan/year) 10 years ago (continuous), BMI (continuous), family history of lung cancer (yes = 1, no = 0), pack-year of smoking (continuous, except for variable of ever smoking), ethanol consumption (mL/week, continuous, except for variable of alcohol drinking status), and study area (Dafeng = 1, Ganyu = 2).

Table 4 shows the effect modification between raw garlic consumption (yes vs. no) and major risk factors for lung cancer. After adjusting for confounding factors, strong interactions were found between raw garlic consumption and ever smoking on both additive scale (SI = 0.70; 95% CI, 0.57–0.85) and multiplicative scale [ratio of OR (ROR) = 0.78; 95% CI, 0.67–0.90]. A multiplicative interaction was observed between raw garlic consumption and high-temperature cooking oil with an ROR of 0.77 (95% CI, 0.59–1.00).

Discussion

In this population-based case–control study with a large sample size, we found that raw garlic consumption at least twice a week was inversely associated with lung cancer in a Chinese population. The inverse association was strong with a monotonic dose–response pattern. Tobacco smoking, high-temperature cooking oil fume, and intake of frying foods were identified as risk factors for lung cancer. Additive and multiplicative interactions were observed between raw garlic consumption and risk factors on lung cancer.

In addition to the frequency of raw garlic consumption, we have also collected the quantity of raw garlic intake. The frequency of raw garlic consumption less than 2 times per week or 2 times or more per week corresponded to an intake of raw garlic of 8.4 g/week or 33.4 g/week, respectively. Association of the raw garlic intake quantity with lung cancer presents similar pattern as that of raw garlic consumption

Table 3. The association between lung cancer and raw garlic consumption frequency stratified by major factors

	Never[a]	<2 times/week		≥2 times/week		
Stratification variables	Case/control	Case/control	Adjusted OR (95% CI)[b]	Case/control	Adjusted OR (95% CI)[b]	P_{trend}[b]
All raw garlic	704/2,423	594/1,637	0.92 (0.79–1.08)	126/483	0.56 (0.44–0.72)	<0.001
Study area						
Dafeng	515/1,954	101/520	0.71 (0.56–0.92)	9/59	0.43 (0.20–0.91)	0.001
Ganyu	189/469	493/1,117	1.15 (0.94–1.42)	117/424	0.66 (0.50–0.88)	0.013
Tobacco smoking						
Never smoker	194/1,095	165/591	0.95 (0.72–1.26)	35/174	0.67 (0.43–1.05)	0.137
All smokers	510/1,328	429/1,046	0.87 (0.73–1.05)	91/309	0.56 (0.42–0.74)	0.000
<30 y	129/575	119/416	0.97 (0.69–1.36)	14/97	0.42 (0.22–0.80)	0.046
≥30 y	381/753	310/630	0.86 (0.69–1.08)	77/212	0.58 (0.41–0.80)	0.002
Alcohol drinking status						
Never or seldom	427/1,572	343/940	0.98 (0.80–1.19)	67/270	0.59 (0.42–0.81)	0.010
Often	277/851	251/697	0.86 (0.67–1.10)	59/213	0.56 (0.38–0.82)	0.005
Factory nearby						
No	571/2,076	533/1,497	0.98 (0.83–1.16)	112/448	0.60 (0.46–0.78)	0.002
Yes	120/301	53/121	0.73 (0.45–1.17)	13/28	0.37 (0.16–0.89)	0.024
High-temperature cooking oil						
No	420/1,687	410/1,169	1.02 (0.84–1.24)	81/338	0.57 (0.41–0.78)	0.006
Yes	284/736	184/468	0.80 (0.62–1.03)	45/145	0.57 (0.38–0.85)	0.004
Consumption of fried food						
No	455/1,714	163/672	0.81 (0.65–1.02)	33/153	0.64 (0.41–0.98)	0.016
Yes	249/709	431/965	0.92 (0.74–1.14)	93/330	0.49 (0.36–0.67)	<0.001
Poor ventilation in kitchen						
No	288/1,080	222/659	0.92 (0.72–1.18)	48/205	0.52 (0.35–0.78)	0.007
Yes	416/1,343	372/978	0.92 (0.75–1.12)	78/278	0.58 (0.42–0.79)	0.003
Family history of lung cancer						
No	661/2,343	572/1,613	0.92 (0.79–1.08)	123/477	0.57 (0.44–0.73)	<0.001
Yes	43/80	22/24	1.09 (0.48–2.46)	3/6	0.26 (0.04–1.63)	0.430
Green tea drinking						
No	528/1,790	358/950	0.86 (0.71–1.04)	66/288	0.44 (0.32–0.60)	<0.001
Yes	128/430	210/584	1.11 (0.83–1.50)	48/172	0.77 (0.50–1.19)	0.410
Exercise 10 years ago						
No	608/2,074	410/1,148	0.84 (0.70–1.00)	93/321	0.54 (0.40–0.72)	<0.001
Yes	96/349	184/489	1.28 (0.92–1.77)	33/162	0.67 (0.41–1.10)	0.332

[a]The reference group.
[b]Adjusted on age (continuous), gender (male = 1, female = 0), education level (illiteracy = 1, primary = 2, middle = 3, high = 4, college = 5), income (Yuan/year) 10 years ago (continuous), BMI (continuous), family history of lung cancer (yes = 1, no = 0, except for variable of family history of lung cancer), pack-year of smoking (continuous, except for variable of tobacco smoking), ethanol consumption (mL/week, continuous, except for variable of alcohol drinking status), and study area (Dafeng = 1, Ganyu = 2, except for variable of study area).

frequency (data not shown). Information on garlic in the other spices was not included in the questionnaire because garlic is not a common ingredient in the spices in Jiangsu Province of China. In stratified analyses, a borderline inverse association of raw garlic consumption with lung cancer risk was observed among never smokers, which is most likely explained by small sample size of nonsmoking cases.

There has been only one recently published paper on the inverse association between raw garlic consumption and lung cancer in Chinese population (26). This hospital-based study, including 226 female lung cancer cases and 269 female healthy controls in Fujian Province, southern China, reported an inverse association between consumption of raw garlic and lung cancer (1–2 times/week adjusted OR = 0.79; 95% CI, 0.49–1.28; >2 times/week adjusted OR = 0.37; 95% CI, 0.16–0.84). The study used the same questionnaire designed for our study and was largely on female nonsmokers (222 cases and 268 controls). It was not able to evaluate

Table 4. The effect modification of lung cancer risk between raw garlic consumption and major risk factors

Variables	Raw garlic consumption	Case/control	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Pack-years of smoking				
≥30 y	No	381/753	1.00	1.00
≥30 y	Yes[b]	387/842	0.91 (0.77–1.08)	0.68 (0.56–0.83)
<30 y	No	129/575	0.44 (0.35–0.56)	0.38 (0.30–0.48)
<30 y	Yes	133/513	0.51 (0.41–0.64)	0.34 (0.26–0.43)
Never	No[c]	194/1095	0.35 (0.29–0.43)	0.21 (0.17–0.27)
Never	Yes	200/765	0.52 (0.42–0.63)	0.24 (0.19–0.31)
Interaction[a]	Additive:	RERI = −0.40 (95% CI, −0.60–−0.20)		
		AP = −0.21 (95% CI, −0.32–−0.09)		
		SI = 0.70 (95% CI, 0.57–0.85)		
	Multiplicative:	ROR = 0.78 (95% CI, 0.67–0.90)		
High-temperature cooking oil				
Yes	No[b]	284/736	1.00	1.00
Yes	Yes	229/613	0.97 (0.79–1.19)	0.74 (0.59–0.92)
No	No	420/1,687	0.65 (0.54–0.77)	0.71 (0.59–0.85)
No	Yes[c]	491/1,507	0.84 (0.71–1.00)	0.68 (0.56–0.82)
Interaction[a]	Additive:	RERI = 0.35 (95% CI, 0.04–0.65)		
		AP = 0.23 (95% CI, 0.04–0.43)		
		SI = 3.56 (95% CI, 0.42–30.46)		
	Multiplicative:	ROR = 0.77 (95% CI, 0.59–1.00)		
Consumption of fried food				
Yes	No[b]	249/709	1.00	1.00
Yes	Yes	524/1,295	1.15 (0.97–1.38)	0.91 (0.74–1.11)
No	No	455/1,714	0.76 (0.63–0.90)	0.82 (0.68–1.00)
No	Yes[c]	196/825	0.68 (0.55–0.84)	0.61 (0.48–0.76)
Interaction[a]	Additive:	RERI = −0.20 (95% CI, −0.59–0.18)		
		AP = −0.12 (95% CI, −0.36–0.11)		
		SI = 0.76 (95% CI, 0.47–1.23)		
	Multiplicative:	ROR = 1.23 (95% CI, 0.94–1.61)		

[a]Adjusted on age (continuous), gender (male = 1, female = 0), education level (illiteracy = 1, primary = 2, middle = 3, high = 4, college = 5), income (Yuan/year) 10 years ago (continuous), BMI (continuous), family history of lung cancer (yes = 1, no = 0), pack-year of smoking (continuous, except for variable of ever smoking), ethanol consumption (mL/week, continuous), and study area (Dafeng = 1, Ganyu = 2).
[b]The joint effects category for further estimation of additive interaction.
[c]The reference category for measures of interaction on additive scale.

the potential interactions between raw garlic consumption and active smoking on the development of lung cancer due to small sample size. However, the observed associations in Fujian study are consistent with our observation.

In the published literature, findings are inconsistent as to the role of garlic supplement against lung cancer. A prospective cohort study in the Netherlands with a total of 484 lung cancer cases reported no obvious association between lung cancer and garlic together with any other supplement use ($n = 13$ cases), compared with any other supplement use. However, lung cancer was found to be positively associated with exclusively garlic supplements use ($n = 23$ cases), compared with no supplements use (27). This positive association may be caused by limited number of cases in the exposure categories and may be confounded by other factors (28). The European Prospective Investigation into Cancer and Nutrition reported protective effects of vegetable and fruit intake on lung cancer; however, specific analysis on raw garlic intake was not conducted (29). A case–control study in Hawaii reported a null association between garlic intake and lung cancer risk with 582 case–control pairs (30). Protective effect of garlic consumption was observed epidemiologically on the development of cancers of the colon, prostate, esophagus, larynx, oral cavity, ovary, and kidney (41).

A protective effect of raw garlic consumption on lung cancer is supported by in *vitro* and animal experimental studies (21–25). Several mechanisms have been proposed to explain the chemopreventive effects of garlic and related OSCs, including inhibition of mutagenesis by inhibiting the metabolism, blockage of DNA adduct formation, free-radical scavenging, effects on cell proliferation and tumor growth, and modulation of immune responses (42). The volatile oil with effective OSCs are largely excreted via lung that might be related to above reviewed mechanisms or functions, in addition to its role in infection control, inflammation reduction, and probable protection of lung from carcinogens such as polycyclic aromatic hydrocarbons. These experimental evidences are supportive for the hypothesis of the protective effects of raw garlic consumption against lung cancer.

Consistent with previous studies, tobacco smoking, factory nearby caused air pollution, and hereditary factors are risk factors of lung cancer. High-temperature cooking oil, fried foods, and bad ventilation in kitchen were found to be positively associated with lung cancer in our study. Consistent with the conclusion on green tea drinking and lung cancer from our recent meta-analysis (OR = 0.66; 95% CI, 0.49–0.89) (43), a reverse association was observed between green tea drinking and risk of lung cancer in this study.

Similar to all case–control studies, selection bias and information bias may exist in our study. To minimize selection bias, we adopted a population-based case–control study design. Cases were identified from the tumor registry rather than from hospitals, whereas healthy controls were selected randomly from the same source population as the cases. Because raw garlic consumption was not a known risk or protective factor for lung cancer, differential recall bias can be limited. However, nondifferential recall or interview bias may still exist, which might lead to underestimation of observed association toward null, making our observed association conservative. In this study, we have a relatively low participation rate (46.3%) and a low proportion of pathologic diagnosis (17%) among cases because most of cases were diagnosed at an advanced stage without surgical treatment. This may lead to potential selection bias by including patients with less severe lung cancer and make the analysis by pathologic type of lung cancer impossible. BMI was calculated on the basis of the measured weight and height at the time of interview, which might lead to a reverse causality. Potential confounding factors also have been considered on the basis of prior knowledge and confounding assessment, and adjusted in the multivariate analysis. We have also adjusted for dietary variables such as fruit, vegetables, red meat, and frying foods; however, no significant changes in ORs were observed. Sensitivity analysis indicated that study area (Dafeng or Ganyu), rather than smoking and other factors, was the major cause of the difference between crude and adjusted ORs due to different garlic consumption patterns. Despite potential limitations, the current study is population based with a large sample size (1,424 cases and 4,543 controls). The epidemiologic data were collected with a comprehensive questionnaire, and a quality control procedure in place. The study is able to evaluate both main associations with raw garlic consumption and potential interactions with other risk/protective factors in a Chinese population.

In conclusion, protective association between consumption of raw garlic and lung cancer has been observed in present study with a clear dose–response pattern, suggesting that raw garlic consumption may potentially serve as a chemopreventive agent for lung cancer. Effective components in garlic in lung cancer chemoprevention warrant further in-depth investigation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Wu, Z.-F. Zhang, J.-K. Zhao
Development of methodology: M. Wu, Z.-F. Zhang, J.-K. Zhao
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Wu, X.-F. Zhang, X.-S. Wang, A.-M. Liu, Z.-F. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Z.-Y. Jin, M. Wu, R.-Q. Han, J.-Y. Zhou, Z.-F. Zhang, J.-K. Zhao
Writing, review, and/or revision of the manuscript: Z.-Y. Jin, M. Wu, X.-F. Zhang, X.-S. Wang, A.-M. Liu, Q.-Y. Lu, Z.-F. Zhang, J.-K. Zhao
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.-Q. Han, X.-F. Zhang, X.-S. Wang, A.-M. Liu
Study supervision: M. Wu, R.-Q. Han, J.-K. Zhao

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