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Raw garlic consumption and lung cancer in a Chinese population

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Abstract

Background—Evidence of anti-cancer properties of garlic for different cancer sites has been reported previously in *in-vitro* and *in-vivo* experimental studies but there is limited epidemiological evidence on the association between garlic and lung cancer.

Methods—We examined the association between raw garlic consumption and lung cancer in a case-control study conducted between 2005 and 2007 in Taiyuan, China. Epidemiological data was collected by face-to-face interviews from 399 incident lung cancer cases and 466 healthy controls. We used unconditional logistic regression models to estimate crude and adjusted odds ratios (aOR) and their 95% confidence intervals (CI). Adjusted models controlled for age, sex, average annual household income 10 years ago, smoking, and indoor air pollution.

Results—Compared to no intake, raw garlic intake was associated with lower risk of development of lung cancer with a dose-response pattern (aOR for <2 times per week = 0.56, 95% CI: 0.39–0.81 and aOR for ≥2 times per week = 0.50, 95% CI: 0.34–0.74; $P_{trend} = 0.0002$). Exploratory analysis showed an additive interaction of raw garlic consumption with indoor air pollution and with any supplement use in association with lung cancer.

Conclusions—The results of the current study suggest that raw garlic consumption is associated with reduced risk of lung cancer in a Chinese population.

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Impact—This study contributes to the limited research in human population on the association between garlic and lung cancer and advocates further investigation into the use of garlic in chemoprevention of lung cancer.

Keywords

Lung cancer; Garlic; Raw garlic; *Allium sativum*; Chinese population

Introduction

Garlic (*Allium sativum*) was used among several ancient civilizations across the world including Egypt (references as early as 3000 B.C.), Greece, Rome, India and China to treat various ailments including poisoning, respiratory and gastric ailments, abnormal growths, headache, insomnia and depression (1-3). In traditional Chinese medicine, garlic is used to improve cardiovascular health and immunity as well as to treat cancer (2, 4). Garlic was used in daily Chinese diet since around 2000 B.C. or earlier where it was consumed especially with raw meat (2). Currently, garlic is used as a popular spice in China, which is the largest producer and exporter of garlic (5).

Garlic is rich in organo-sulfur compounds (OSCs), which are responsible for most of its therapeutic properties including antibacterial, anti-protozoal, antifungal, hypolipidemic, antiatherosclerotic and anticancer properties (6, 7). The major OSCs that contribute to the anticancer properties of garlic include allicin, allixin, diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), S-allyl cysteine allylmercaptan, allylmethylthiol, allylmethyltrisulfide and ajoene (8-10). Several mechanisms including inhibiting cancer initiation, suppressing cancer promotion and preventing oxidative damage have been attributed to the anti-cancer properties of garlic (7-9, 11, 12). *In-vitro* and *in-vivo* experimental studies provided evidence for the anti-cancer properties of garlic against stomach, liver, colon, prostate, skin, bladder, breast and lung cancer (7, 13-17). Case-control studies conducted in different populations reported an inverse association between garlic consumption (raw/cooked) and colorectal, prostate, and head and neck cancers (18-20). However, Dutch prospective cohort studies showed no inverse association between garlic supplement intake and gastric, colorectal breast and lung cancers (21-24). Thus, consistent epidemiological evidence on the protective effects of garlic against different cancers is lacking.

In 2012, lung cancer accounted for 13% of total cancer cases and 19% of total cancer deaths worldwide (25). In China, lung cancer is the most common cancer in incidence and mortality (2011 statistics) with a higher age-standardized mortality of 28.0 per 100,000, compared to the world population (19.7 per 100,000) (25, 26). In the past 30 years, lung cancer mortality in China increased by 464.84% (27). Smoking, exposure to secondhand smoke, and air pollution (both outdoor and from indoor household fuel combustion) are the major risk factors of lung cancer in China (27). Evidence from previous epidemiological studies suggest that factors that may be protective against lung cancer are mainly related to diet, especially higher consumption of fruits and vegetables (28-30).

The existing epidemiological evidence of the association between garlic and lung cancer (Table 1) is limited and inconsistent (21, 31-35). Review of previous literature indicates that raw/cooked garlic rather than a more processed form (e.g. supplements) was inversely associated with the risk of cancer (36). Additionally, heating garlic seems to drastically diminish its anticarcinogenic properties (37-40). Therefore, raw garlic may potentially possess better anti-cancer properties compared to heated/cooked/processed garlic. Compared to the Chinese, raw garlic intake among other populations is very low, which makes it difficult to analyze disease associations (36). For example, in 1995, the annual average consumption of fresh garlic per person in Cangshan County, Shangdong Province, China was 6 kg while it was only 0.8 kg in the U.S (41). Thus, the Chinese population is probably better suited for studying the association between garlic intake and cancer.

Only two recent case-control studies in Chinese population investigated the association between raw garlic consumption and lung cancer. Both studies reported that higher consumption of raw garlic (2 or more times per week) was protective against lung cancer (31, 33). In the current study, we analyzed data collected from a case-control study conducted in Taiyuan City, Shanxi Province, China and sought to replicate the association between raw garlic consumption and lung cancer. In addition, we explored for interaction between major risk factors and raw garlic consumption in association with lung cancer.

Materials and Methods

Study population

Cases were recruited between 2005 and 2007 from Shanxi Tumor Hospital, where about 70% of cancer patients from Taiyuan city sought treatment. Eligible cases were newly diagnosed lung cancer patients who were aged 20 years or older, lived in Taiyuan city for 10 years or more, in stable medical condition and willing to participate in the study. Controls were randomly selected from resident lists of 13 communities covering most of Taiyuan city to match cases according to the distribution of age and gender. Eligibility criteria for controls were same as the cases but controls had no history of cancer or any other serious chronic disease. A total of 399 cases (89% response rate) and 466 controls (85% response rate) participated in the study. Informed consent was obtained from study participants before completing the study questionnaire. A detailed description regarding participant recruitment was previously published (42).

Data collection

Epidemiologic data was collected by trained study personnel using a structured questionnaire to conduct face-to-face interviews of all cases at the hospital and all controls at community health centers. The questionnaire included information on demographic characteristics, residence and housing history, living and cooking habits, smoking, alcohol drinking, tea drinking and personal and family medical history. "Ever smokers" were defined as those who smoked at least 100 cigarettes during their lifetime. Dietary intake 1 year ago was evaluated using 96-item food frequency questionnaire and other questions on specific items. Raw garlic intake was assessed by asking "How often do you eat raw garlic?" Participants chose one of the following responses: (1) never (2) occasionally (<2 times/

week) (3) often (≥ 2 times/week) (4) do not know. We assessed overall exposure to indoor air pollution (IAP) 10 years prior to the date of interview by creating an IAP index, which was based on an individual's exposure to five major risk factors including solid fuel use for cooking and heating, ventilation in kitchen, opening of windows in winter and secondhand smoking. Exposure to each risk factor was scored as '1' and based on the number of the above five risk factors that an individual was exposed to; an IAP index of 0-5 was assigned.

Statistical analysis

We used chi-square and *t* tests to test the differences in distribution of selected demographic characteristics (age, sex, education, average annual household income 10 years ago), body mass index (BMI), smoking, IAP exposure (IAP index of 0 = none, 1-2 = low and 3-5 = high) alcohol drinking, tea drinking and supplement use (intake of one or more of the following – vitamin A, beta-carotene, vitamin C, vitamin E, calcium, selenium, zinc or multivitamin) among cases and controls. We also tested differences in the distribution of the above characteristics by raw garlic consumption (never, < 2 times per week and ≥ 2 times per week) using chi-square and one-way ANOVA tests. For the analysis in the current study, we excluded 7 participants who did not report their intake of raw garlic. Unconditional logistic regression models were used to estimate crude and adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the association between raw garlic intake and lung cancer. Based on prior knowledge and review of previous relevant literature, selected covariables including education, average annual household income 10 years ago, BMI, pack years of smoking, IAP, alcohol drinking, tea drinking and supplement use were tested for association with the exposure and/or the disease in the study population. Education, BMI, pack years of smoking, IAP and supplement use were associated with lung cancer but not with raw garlic intake. Average annual household income 10 years ago was the only variable that was associated with both raw garlic intake and lung cancer. Age and sex being frequency matching variables, were included in the multivariate model. We generated two multivariate models to present the results of logistic regression. Model 1 adjusted for age, sex and average annual household income. Model 2 additionally adjusted for smoking and IAP considering that they were among the strongest risk factors for lung cancer in the Chinese population. The results from a saturated multivariable model that included all covariables were similar to the results from Model 2. We chose to use Model 2 as the final multivariate model. The association between raw garlic consumption and lung cancer was estimated in the overall population as well as in subgroups of age, sex, smoking, IAP, alcohol drinking, tea drinking, supplement use, and by histological subtypes of lung cancer. We also evaluated for multiplicative and additive interaction of raw garlic consumption with age (0 = < 55 years, 1 = ≥ 55 years), smoking status (0 = never, 1 = ever), IAP (0 = no/low, 1 = high), alcohol drinking (0 = no, 1 = yes), tea drinking (0 = never, 1 = ever) and supplement use (0 = no, 1 = yes) in association with lung cancer. Raw garlic consumption was operationalized as 0 = “never” and 1 = “any” intake for interaction analysis. Multiplicative interaction was evaluated by including the main effect variables and their product term in logistic regression models. A ratio of odds ratios (ROR) estimate of the product term was considered statistically significant if the confidence interval did not include '1.00'. Additive interaction was assessed by calculating relative excess risk of interaction (RERI) and inclusion of '0.00'

within the CIs of RERI estimate indicated absence of more than additivity or no additive interaction. All analyses were performed using SAS 9.4 software.

Results

Approximately 56% of study participants were aged 55 years or older and approximately half of the participants were males. Differences in distribution of study characteristics between cases and controls are presented in Table 2. Cases had a higher mean age and a higher proportion of cases were exposed to high IAP. Education, average annual household income 10 years ago, BMI, and supplement use were higher among controls. Approximately 55% of cases (93% males and 17% females) were ever-smokers compared to 39% of controls (71% males and 6% females). The smoking prevalence among female cases is similar to that observed in previous studies in Chinese population (43-45).

Table 3 shows the distribution of study characteristics by participants' raw garlic consumption. We did not find differences in the distribution of any of the study characteristics except for average annual household income 10 years ago. High income participants (≥ 2500 Renminbi) consumed higher amounts of raw garlic (≥ 2 times/week) compared to those with lower income. Smoking exposure did not differ by raw garlic consumption.

The overall association of raw garlic consumption with lung cancer in crude and adjusted models is presented in Table 4. Raw garlic consumption in all categories (any intake, < 2 times per week, ≥ 2 times per week) was inversely associated with lung cancer in the crude and both the multivariable models after adjusting for potential confounders. Compared to no intake, raw garlic consumption was inversely associated with lung cancer (< 2 times/week: aOR = 0.56, 95% CI: 0.39–0.81; ≥ 2 times/week: aOR = 0.50, 95% CI: 0.34 – 0.74) with a dose-response relationship ($P_{\text{trend}} = 0.0002$). We did not find notable differences between the results from the two multivariate models.

Table 5 shows the association between raw garlic consumption and lung cancer among any garlic consumers as well as those who consumed < 2 times/week and ≥ 2 times/week, stratified by age, sex, smoking status, IAP, alcohol drinking, tea drinking, supplement use and association with specific histo-pathological subtypes of lung cancer. The association between raw garlic consumption and lung cancer was stronger in the younger age group, among females and those exposed to IAP, whereas the association did not differ by smoking status, alcohol drinking and tea drinking. The association with adenocarcinoma and squamous cell carcinoma subtypes was statistically significant. When these analyses were further stratified by sex, the associations seemed to be more prominent among women (Supplementary Table S1). However, these observations may not be sufficient to draw explicit conclusions because of the small sample sizes within the strata.

Figure 1 depicts the results of the exploratory interaction analyses between raw garlic consumption and selected risk factors in association with lung cancer. We observed additive interaction between IAP and raw garlic consumption (aRERI = 0.37, 95% CI: 0.05–0.68) as

well as supplement use and raw garlic consumption (aRERI = 0.41, 95% CI: 0.08–0.74) in association with lung cancer.

Discussion

In the current study, we observed that raw garlic consumption was inversely associated with lung cancer with a dose-response relationship. The association between raw garlic consumption and lung cancer did not differ by smoking status, alcohol drinking and tea drinking. We observed additive interaction between raw garlic consumption and IAP as well as between raw garlic consumption and supplement use in association with lung cancer.

Only two recent publications examined the association between raw garlic consumption and lung cancer and observed statistically significant inverse associations (31, 33). A case-control study conducted in Fujian Province, China reported that compared to no intake, consuming raw garlic more than 2 times per week was inversely associated with lung cancer (aOR = 0.37, 95% CI: 0.16–0.84). This association was slightly stronger than what we observed in the current study. The smaller sample size (226 cases and 269 controls), consisting of primarily non-smoking women and the assessment of raw garlic consumption (no consumption, 1-2 times/week, >2 times/week) that is somewhat different from the current study could have contributed to the differences. The Fujian study did not report an association in the lower raw garlic consumption category (1-2 times/week).

Another case-control study with larger sample size (1424 cases and 4543 controls) conducted in Jiangsu Province, China reported an inverse association between raw garlic intake and lung cancer among those who consumed raw garlic ≥ 2 times/week (aOR = 0.56, 95% CI: 0.44–0.72) (31). This association was similar to what we found in the current study. Similar to the Fujian study, the Jiangsu study did not find an association in the low garlic consumption category (<2 times/week). This may reflect the differences in the consumption of raw garlic in different geographic regions in China. The percentage of ever-garlic consumption was lower in the Jiangsu study (47.6%) compared to the current study (55.83%) and the use of garlic as an ingredient in the spices was not common among the residents of that province (31). Although there are some differences, the current study reiterated the findings of the previous two studies that raw garlic consumption of 2 or more times per week may be protective against lung cancer.

In the current study, we observed a slightly stronger association between raw garlic consumption and lung cancer among women and the younger participants (<55 years). Differences in smoking characteristics may have played a role in this observation. A dose-response relationship between raw garlic consumption and lung cancer was observed in never-smokers, but not in ever smokers. Approximately 90% of women were never-smokers and the majority of participants in the younger age group were women and never-smokers. Although it may seem that the protective association between raw garlic consumption may be restricted to certain subgroups like women and never-smokers, the observations from the stratified analysis may not be sufficient to derive definite conclusions because of the limited sample size in the individual strata.

We observed that the association between raw garlic consumption and lung cancer was modified by IAP and supplement use on an additive scale. IAP is a major risk factor for lung cancer in China, with the major sources being fuel used for cooking and indoor heating (27, 42). Our finding indicates that the reduced risk of lung cancer associated with low/no exposure to IAP and consumption of raw garlic might be greater than the risk reduction associated with any one of the factors alone. We also observed an additive interaction between supplement use and raw garlic consumption in association with lung cancer. A recent review of clinical trials that investigated drugs for preventing lung cancer suggested that intake of vitamin and mineral supplements either alone or in combination do not reduce either incidence or mortality due to lung cancer (46). Other studies did not report consistent evidence for associations between lung cancer and the supplements taken by the majority of the participants in the current study (vitamin C, vitamin E and calcium) who reported any supplement use (47-50). We do not have additional information to attribute the observed additive interaction between supplement use and raw garlic intake to any single supplement. Further targeted investigation with larger study samples is necessary to confirm potential interactions of garlic with other risk or protective factors in association with lung cancer.

Although the anti-cancer properties are mainly attributed to the bioactive OSCs, garlic contains other nutrients including flavonoids, oligosaccharides, arginine and potassium, vitamin C and selenium that may contribute to its overall beneficial effects (51, 52). The major mechanisms contributing to the anti-cancer potential of garlic are: (i) inhibition of cancer initiation by suppressing the formation, intercepting metabolic activation and enhancing enzyme-detoxification of carcinogens (e.g. nitrosamines) as well as by inhibiting the formation of DNA-adducts; (ii) blocking cancer promotion through anti-proliferating activities including regulation of cell cycle arrest in G2/M phase and promoting apoptosis in cancer cells; (iii) antioxidant activity formation and/or scavenging of free radicals. Other mechanisms include the inhibition of cancer cell growth by modification of histone acetylation, inhibition of angiogenesis, immunomodulation and anti-inflammatory activity (8-12, 51, 53-56). The results of the current study align well with the anticancer mechanisms of garlic as described. When garlic is ingested, the active volatile compounds that are released in the stomach diffuse into the lung tissues (4) where the OSCs may act through the mechanisms described above to protect against lung cancer. Epidemiological evidence based on results of meta-analyses show that higher consumption of fruits and vegetables may also protect against lung cancer (16, 30, 57). The association between raw garlic consumption and lung cancer seems to be stronger than the association with consumption of fruits [pooled OR = 0.80; 95% CI: 0.74–0.88] and consumption of vegetables [pooled OR = 0.74; 95% CI: 0.67–0.82] (57). The numerous anti-cancer properties of garlic including high antiproliferative and antioxidant properties (58), which are mediated through multiple mechanisms, may explain the potential stronger protection effect of garlic alone against lung cancer. Further studies are needed to substantiate the evidence observed in the current study.

The current study has the following limitations: *1. Sample size:* Our study results are based on a relatively small sample size but they do reiterate the findings from previous published studies regarding the relationship between raw garlic consumption and lung cancer. Our exploration for interaction with known risk factors for lung cancer may have been affected by the small sample sizes in subgroup analyses. Hence, we suggest interpreting the

interaction results from the current study with caution. Raw garlic consumption may differ considerably by geographic region. Jin et al. (2013) reported that garlic consumption patterns differed even between the two counties in the Jiangsu province where the study was conducted, which may have influenced the magnitude of adjusted association compared to the crude model, more than smoking and other factors (31). Thus, more studies involving different populations and larger study samples are justified to verify the association between raw garlic consumption and lung cancer.

2. Bias: As in any case-control study, the results of the current study may have been affected by bias. Incident lung cancer cases were recruited from Shanxi Tumor Hospital, visited by 70% of the cancer patients from Taiyuan city for treatment, while controls were selected from 13 communities of the same source population. The response rates for both cases and controls were high (89% for cases and 86% for controls). These design measures may have contributed to minimize selection bias. There are two possibilities for information bias. Firstly, study personnel conducted face-to-face interviews with lung cancer patients in the hospital and controls were interviewed in community centers. The use of structured questionnaires and trained interviewers would have minimized any potential bias. Secondly, differential recall of raw garlic intake by cases and controls could have resulted in biased estimates. However, in both instances, as raw garlic intake was not thought to be associated with lung cancer at the time of data collection (31), any potential information bias would be non-differential. This may have attenuated the estimate towards the null, which would make the current observed estimates conservative.

3. Cooked garlic intake: We did not assess consumption of cooked garlic. Heating garlic seems to drastically diminish its anticarcinogenic properties (8, 38, 40). If we assume that a certain amount of anti-cancer potential is preserved in cooked garlic and participants in the “never raw garlic” group actually ate cooked garlic, it may lead to exposure misclassification. If the misclassification was non-differential, the association between raw and cooked garlic and lung cancer would probably bias towards the null. Alternatively, higher proportion of cases than controls being misclassified would probably weaken the association whereas a higher proportion of controls than cases being misclassified would probably make the association stronger than the current observations. Considering the limited anti-cancer potential, we do not expect the association of raw and cooked garlic with lung cancer to significantly deviate from the current observed results.

4. Raw garlic intake quantity: Quantity of raw garlic intake was not assessed in the current study. A previous study in a Chinese population (Jiangsu Province) reported a similar pattern of association between raw garlic intake quantity and lung cancer when compared to the association using raw garlic consumption frequency (results were not presented) (31). Although, we cannot make distinct conclusions based on the current study without the required data, we do not expect this to significantly impact our study results.

Despite the above-mentioned limitations, the current study provides epidemiological evidence to substantiate the protective effect of raw garlic against lung cancer, which have been indicated in previous *in-vitro* studies that investigated the effects of garlic OSCs on human lung cancer cell lines (e.g. Calu-1, A-549 cells) (14-17, 59, 60) as well as in animal models (61-63). Garlic OSCs were successfully tested for chemotherapy of cancers of various organs including breast (13), prostate (64) and colon (65). Currently, many OSCs are being tested for their potential role in lung cancer treatment (14). A randomized phase IIb

trial conducted in former and current smokers with a history of at least 30 pack years showed that participants who received the OSC anethole dithiolethione (ADT) as treatment had a higher reduction in progression of bronchial dysplasia and/or appearance of new lesions compared to those who received a placebo (66). Hence, garlic and garlic derived OSCs show promise for lung cancer chemoprevention and chemotherapy. Further intervention trials and prospective studies are needed to verify the feasibility of using garlic or garlic OSCs in lung cancer prevention. In this regard, it is important to develop stable OSCs that can be successfully used in chemotherapy. Consuming raw garlic itself might provide a cost-effective method to prevent lung cancer. It would certainly seem more beneficial to promote intake of garlic as part of a healthy daily diet among never smokers compared to ever smokers. However, the magnitudes of association in the current and previous study (31) indicate that raw garlic consumption may be protective against lung cancer among never-smokers as well as ever smokers.

Among Chinese men, the prevalence of cigarette smoking is extremely high (52.9%) (67) and the percentage of ever smokers who have quit (12.6%) (67) is among the lowest in the world (67, 68). Encouraging smoking cessation through programs and policies reduces disease risk and helps to protect non-smokers from the deleterious effects of secondhand smoke (69-71) and should be the first priority. It would also be prudent to promote consumption of raw garlic as a preventive approach against lung cancer, among both ever smokers and never-smokers.

In conclusion, our results indicate that raw garlic consumption may protect against lung cancer in a Chinese population. As evidence from epidemiological studies can be utilized to promote dietary modification in lung cancer prevention, further studies are warranted to confirm the observed association among different populations and with larger study sample sizes to establish the role and utility of garlic in lung cancer chemoprevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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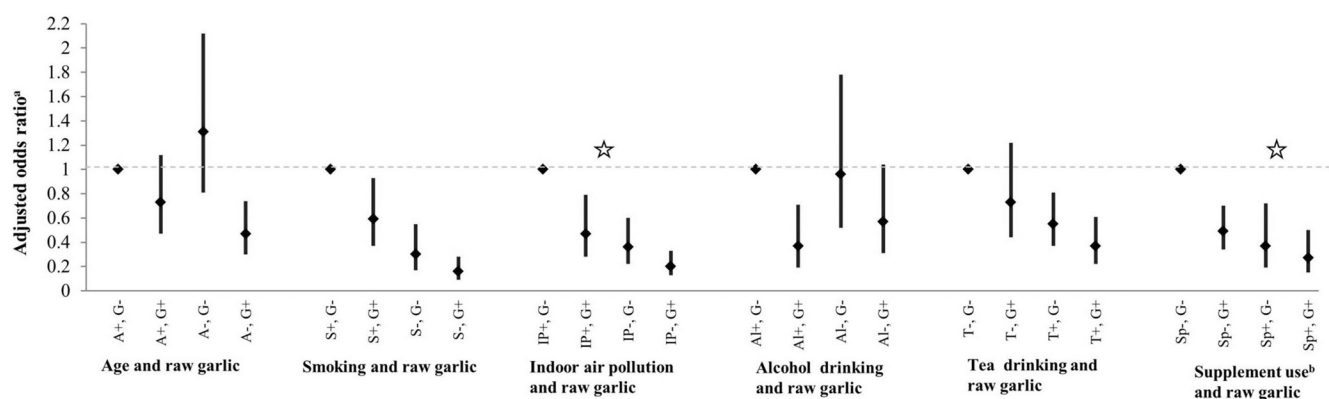


Figure 1.

Charts depicting the joint effects of raw garlic consumption and selected risk factors in association with lung cancer. G+: any raw garlic intake; G-: no raw garlic intake; A+: age ≥ 55 years; A-: age < 55 years; S+: ever smokers; S-: never smokers; IP+: high indoor air pollution; IP-: low/no indoor air pollution; Al+: alcohol ever drinkers; Al-: alcohol never drinkers; T+: Tea ever drinkers; T-: Tea never drinkers; Sp+: supplement users; Sp-: Supplement non-users. ^a adjusted for age (in years, except for interaction with age), sex, average household income 10 years ago ($< 1000 = 1$, $1000-2499 = 2$, $2500-4999 = 3$, $\geq 5000 = 4$), pack years of smoking (continuous, except for interaction with smoking), and indoor air pollution (an index of 0 = none, 1-2 = low and 3-5 = high indoor air pollution, except for interaction with indoor air pollution); ^b supplemental use includes intake of one or more of the following: vitamin A, beta-carotene, vitamin C, vitamin E, calcium, selenium, zinc or multivitamins. ☆ additive interaction between indoor air pollution and raw garlic consumption (RERI = 0.37, 95% CI: 0.05–0.68) as well as supplement use and raw garlic consumption (RERI = 0.41, 95% CI: 0.08–0.74)

Table 1
Review of relationship between garlic consumption and lung cancer from published epidemiological studies

Reference	Study design	Study population	Study sample	Garlic (form)	Garlic consumption	Results	Comments
Jin et al. (2013) ^a	Case-control study (population-based multi-center study)	China(Jiangsu province)	1424 cases / 4543 controls	Raw garlic	Never <2 times/week ≥2 times/week	<i>Estimated Odds ratio</i> 1.00 0.92 (0.79–1.08) 0.56 (0.44–0.72) $P_{trend} = <0.001$	Adjusted for age, gender, education, income, BMI, family history, smoking, alcohol drinking and study area.
Lin et al. (2012) ^b	Case-control study	China -women (Fujian province)	226 cases / 269 controls matched on age	Raw garlic	No consumption 1-2 times/week > 2 times/week	<i>Estimated odds ratio</i> 1.00 0.79 (0.49–1.28) 0.37 (0.16–0.84)	Adjusted for age, cooking oil fumes, use of fume extractor and environmental tobacco smoke
Satia et al. (2009) ^c	Prospective cohort study	U.S.A. (Washington state)	665lung cancer cases / 76,460 non-lung cancer individuals	Garlic supplement pills (past ten years use)	Non user User	<i>Estimated hazard ratio</i> 1.00 1.09 (0.83–1.34)	- Adjusted for age, gender, education, years smoked, pack years and pack-years squared. - Study examined association of lung cancer risk with various herbal and specialty supplement use during the past ten years
Linseisen et al. (2007) ^d	Prospective cohort study	10 European countries	1126 lung cancer cases / 478,590 cohort members followed	Garlic vegetable	Quintiles of consumption	<i>Estimated hazard risk</i> No association found	- Adjusted for smoking status and duration, education, physical activity at work, intake of red meat, intake of processed meat, height, weight, non-fat energy intake, energy intake from fat and ethanol intake at baseline. - Results from European Prospective Investigation into Cancer and

Reference	Study design	Study population	Study sample	Garlic (form)	Garlic consumption	Results	Comments
Le Marchand et al. (2000) ^e	Case-control study (population based)	Hawaii, U.S.A	582 cases / 582 controls matched on age, sex and ethnicity	Garlic vegetable	Quartiles of consumption Quartile 1 Quartile 2 Quartile 3 Quartile 4 <i>p for trend</i>	<i>Estimated odds ratio</i> 1.00 0.9 (0.6–1.4) 0.8 (0.5–1.2) 0.7 (0.4–1.1) 0.12	- Adjusted for smoking status, duration of smoking, number of cigarettes smoked per day, intakes of β-carotene and saturated fat. - Form of garlic (raw/cooked/other) for consumption was not specified
Dorant et al. (1994) ^f	Case-cohort	Netherlands	484 lung cancer cases / 3123 non-cancer controls	Garlic supplements	No sup ^g use Garlic sup ^a Only Other sup ^a only Garlic and other sup ^a	<i>Estimated rate ratio</i> 1.00 1.78 (1.08–2.92) 1.00 0.93 (0.46–1.86)	Adjusted for age, gender, pack years of current and past smoking, education, history of COPD, onion and leek consumption, vitamin C and beta carotene.

^a reference # 28;^b reference # 30;^c reference # 32;^d reference # 31;^e reference # 29;^f reference # 21;^g sup=supplements

Table 2
Distribution of study characteristics among lung cancer cases and cancer-free controls

Variables	Cases (N=399) N (%)	Controls (N=466) N (%)	<i>p</i> ^a
Age (years)			
≤ 44	59 (14.8)	83 (17.8)	0.07
45 - 54	96 (24.1)	139 (29.8)	
55 - 64	111 (27.8)	116 (24.9)	
≥ 65	133 (33.3)	128 (27.5)	
Mean (SD)	58.1 (11.9)	56.1 (11.3)	0.01
Sex			
Male	202 (50.6)	234 (50.2)	0.90
Female	197 (49.4)	232 (49.8)	
Education			
Illiteracy	43 (10.8)	23 (4.9)	< 0.0001
Primary School	106 (26.6)	81 (17.4)	
Middle School	124 (31.1)	175 (37.5)	
High School	68 (17.0)	120 (25.8)	
College and above	58 (14.5)	67 (14.4)	
Average annual income/person 10 years ago (RMB)^b			
< 1000	104 (26.1)	106 (22.7)	< 0.0001
1000 – 2499	236 (59.1)	197 (42.3)	
2500 – 4999	37 (9.3)	116 (24.9)	
≥ 5000	22 (5.5)	47 (10.1)	
Mean (SD)	1994.5 (2678.9)	2539.4 (3193.7)	0.007
BMI (Kg/m²)			
< 18.5	22 (5.8)	9 (2.0)	< 0.0001
18.5 – 24.9	250 (66.3)	259 (56.3)	
25 – 29.9	90 (23.9)	162 (35.2)	
≥ 30	15 (4.0)	30 (6.5)	
Mean (SD)	23.4 (3.6)	24.8 (3.9)	< 0.0001
Pack years of smoking			
Never smokers ^c	179 (44.9)	285 (61.2)	< 0.0001
< 30	64 (16.0)	107 (22.9)	
≥ 30	156 (39.1)	74 (15.9)	
Indoor air pollution^d			
None	38 (10.8)	90 (19.7)	< 0.0001
Low	145 (41.2)	253 (55.2)	
High	169 (48.0)	115 (25.1)	
Alcohol drinking^e			
Never	298 (74.7)	345 (74.0)	0.83

Variables	Cases (N=399)	Controls (N=466)	<i>p^a</i>
	N (%)	N (%)	
Ever	101 (25.3)	121 (26.0)	
Tea drinking			
Never	242 (60.7)	263 (56.4)	0.21
Ever	157 (39.3)	203 (43.6)	
Supplement use^f			
No	342 (87.0)	355 (77.2)	0.0002
Yes	51 (13.0)	105 (22.8)	

^afrom two sided χ^2 test for categorical variables and from t test for continuous variables. p-values in bold represent statistical significance;

^bRMB = Renminbi, the Chinese currency;

^csmoked less than 100 cigarettes during lifetime;

^dIndoor air pollution exposure was calculated by summarizing participant's exposure to solid fuel for cooking and heating, ventilation in kitchen, opening of windows in winter and second hand smoking (an index of 0 = none, 1-2 = low and 3-5 = high indoor air pollution).

^elifetime alcohol drinking status.

^fsupplement use includes intake of one or more of the following: vitamin A, beta-carotene, vitamin C, vitamin E, calcium, selenium, zinc or multivitamins.

Table 3
Distribution of study characteristics by categories of participants' consumption of raw garlic

Variable	Raw garlic consumption			<i>p</i> ^a
	Never (N=357)	<2 times/week (N=244)	≥2 times/week (N=239)	
	N (%)	N (%)	N (%)	
Age (years)				
≤ 44	53 (14.9)	50 (20.5)	39 (16.3)	0.46
45 - 54	100 (28.0)	65 (26.6)	69 (28.9)	
55 - 64	101 (28.3)	64 (26.3)	55 (23.0)	
≥ 65	103 (28.8)	65 (26.6)	76 (31.8)	
Mean (SD)	57.2 (11.2)	56.1 (11.7)	56.7 (12.1)	0.53
Sex				
Male	175 (49.0)	115 (47.1)	126 (52.7)	0.46
Female	182 (51.0)	129 (52.9)	113 (47.3)	
Education				
Illiteracy	23 (6.4)	16 (6.6)	24 (10.0)	0.48
Primary School	88 (24.7)	45 (18.4)	48 (20.1)	
Middle School	122 (34.2)	94 (38.6)	78 (32.6)	
High School	74 (20.7)	55 (22.5)	53 (22.2)	
College and above	50 (14.0)	34 (13.9)	36 (15.1)	
Average annual household income 10 years ago (RMB)^b				
< 1000	106 (29.7)	53 (21.7)	48 (20.1)	0.0006
1000 – 2499	181 (50.7)	133 (54.5)	106 (44.3)	
2500 – 4999	47 (13.2)	39 (16.0)	58 (24.3)	
≥ 5000	23 (6.4)	19 (7.8)	27 (11.3)	
Mean (SD)	2033.7 (2590.5)	2289.5 (3237.3)	2685.0 (3330.4)	0.04
BMI (Kg/m²)				
< 18.5	17 (4.9)	6 (2.6)	8 (3.5)	0.82
18.5 – 24.9	215 (61.4)	147 (62.8)	137 (59.6)	
25 – 29.9	99 (28.3)	70 (29.9)	73 (31.7)	
≥ 30	19 (5.4)	11 (4.7)	12 (5.2)	
Mean (SD)	23.9 (4.1)	24.2 (3.6)	24.3 (3.7)	0.53
Pack years of smoking				
Never smokers ^c	195 (54.6)	135 (55.3)	124 (51.8)	0.89
< 30	67 (18.8)	46 (18.9)	52 (21.8)	
≥ 30	95 (26.6)	63 (25.8)	63 (26.4)	
Indoor air pollution^d				
None	46 (13.6)	31 (13.6)	46 (20.9)	0.11
Low	162 (47.9)	119 (52.2)	100 (45.5)	
High	130 (38.5)	78 (34.2)	74 (33.6)	

Variable	Raw garlic consumption			<i>p</i> ^a
	Never (N=357)	<2 times/week (N=244)	≥2 times/week (N=239)	
	N (%)	N (%)	N (%)	
Alcohol drinking ^e				
Never	274 (76.8)	188 (77.0)	168 (70.3)	0.14
Ever	83 (23.2)	56 (23.0)	71 (29.7)	
Tea drinking				
Never	212 (59.4)	146 (59.8)	134 (56.1)	0.65
Ever	145 (40.6)	98 (40.2)	105 (43.9)	
Supplement use ^f				
No	294 (83.8)	191 (78.9)	197 (83.5)	0.27
Yes	57 (16.2)	51 (21.1)	39 (16.5)	

^afrom two sided χ^2 test for categorical variables and from ANOVA for continuous variables. p-values in bold represent statistical significance;

^bRMB = Renminbi, the Chinese currency;

^csmoked less than 100 cigarettes during lifetime;

^dIndoor air pollution exposure was calculated by summarizing participant's exposure to solid fuel for cooking and heating, ventilation in kitchen, opening of windows in winter and second hand smoking (an index of 0 = none, 1-2 = low and 3-5 = high indoor air pollution).

^elifetime alcohol drinking status.

^fSupplement use includes intake of one or more of the following: vitamin A, beta-carotene, vitamin C, vitamin E, calcium, selenium, zinc or multivitamins.

Table 4

Association of raw garlic consumption with lung cancer

Raw garlic consumption	Cases (N=392)	Controls (N=448)	cOR (95% CI)	Model 1 ^a aOR (95% CI)	Model 2 ^b aOR (95% CI)
	N (%)	N (%)			
Never	197 (50.3)	160 (35.7)	1.00	1.00	1.00
Any	195 (49.7)	288 (64.3)	0.55 (0.42–0.73)	0.59 (0.44–0.78)	0.52 (0.38–0.72)
< 2 times/week	104 (26.5)	140 (31.3)	0.60 (0.43–0.84)	0.61 (0.44–0.86)	0.56 (0.39–0.81)
≥ 2 times/week	91 (23.2)	148 (33.0)	0.50 (0.36–0.70)	0.56 (0.40–0.80)	0.50 (0.34–0.74)
<i>P</i> _{trend}			<0.0001	0.0006	0.0002

cOR = crude odds ratio aOR = adjusted odds ratio;

^a adjusted for age (years), sex, and average household income 10 years ago (<1000 = 1, 1000–2499 = 2, 2500–4999 = 3, ≥5000 = 4).^b adjusted for pack years of smoking (continuous) and indoor air pollution (an index of 0 = none, 1–2 = low and 3–5 = high indoor air pollution) in addition to the covariates in Model 1.

Table 5
Association between raw garlic consumption and lung cancer stratified by major risk factors

Variable	Never	Any	<2 times/week	≥2 times/week	P_{trend}^a
Age (years)					
<55	88/65	67/156	34/81	33/75	0.40 (0.23–0.72) <0.001
≥55	109/95	128/132	70/59	58/73	0.57 (0.33–0.99) 0.049
Sex					
Males	92/83	103/138	54/61	49/77	0.60 (0.34–1.08) 0.071
Females	105/77	92/150	50/79	42/71	0.43 (0.25–0.75) 0.001
Smoking status					
Never	96/99	82/177	49/86	33/91	0.41 (0.24–0.71) <0.001
Ever	101/61	113/111	55/54	58/57	0.63 (0.28–1.41) 0.063
Indoor air pollution					
None	18/28	20/57	11/20	9/37	0.35 (0.11–1.10) 0.075
Low	74/88	66/153	39/80	27/73	0.45 (0.25–0.82) 0.006
High	88/42	80/72	40/38	40/34	0.62 (0.32–1.19) 0.077
Alcohol Drinking					
No	148/126	146/210	83/105	63/105	0.51 (0.32–0.81) 0.003
Yes	49/34	49/78	21/35	28/43	0.53 (0.23–1.21) 0.078
Tea Drinking					
Never	121/91	117/163	65/81	52/82	0.46 (0.29–0.77) 0.002
Ever	76/69	39/59	39/59	39/66	0.50 (0.26–0.95) 0.019
Supplement use^b					
No	171/123	167/221	86/105	81/116	0.46 (0.30–0.72) <0.001
Yes	23/34	26/64	17/34	9/30	0.76 (0.24–2.35) 0.622
Histo-pathology					
ACC	53/160	54/288	33/140	21/148	0.43 (0.22–0.81) <0.001
SqCC	47/160	42/288	17/140	25/148	0.59 (0.30–1.17) 0.050
SmCC	26/160	31/288	17/140	14/148	0.58 (0.26–1.28) 0.136

Ca/Co = cases/controls; aOR = adjusted odds ratio; ACC = adenocarcinoma, SqCC = squamous cell carcinoma, SmCC = small cell carcinoma.

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^aadjusted for age (in years except for subgroups of age), sex (except for subgroups of sex), average annual household income 10 years ago (<1000 = 1, 1000-2499 = 2, 2500-4999 = 3, ≥5000 = 4), pack years of smoking (continuous, except for subgroups of smoking), and indoor air pollution (an index of 0 = none, 1-2 = low and 3-5 = high indoor air pollution except for subgroups of indoor air pollution);

^bsupplement use includes intake of one or more of the following: vitamin A, beta-carotene, vitamin C, vitamin E, calcium, selenium, zinc or multivitamins. Statistically significant OR estimates and p-values are presented in bold font.