Author Manuscript Published OnlineFirst on May 8, 2013; DOI: 10.1158/1940-6207.CAPR-13-0015
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Raw garlic consumption as a protective factor for lung cancer, a population-based case-control study in a Chinese population

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Running title: Raw garlic consumption and lung cancer

Keywords: lung cancer; garlic consumption; case-control study; China

Financial Support: (the source and number of grants for each author)

This project was supported by Jiangsu Provincial Health Department (RC 2003090); was partially supported by the National Institutes of Health, National Institute of Environmental Health Sciences, National Cancer Institute, Department of Health and Human Services, Grants ES06718, ES01167, CA90833, CA077954, CA09142, CA96134, DA11386; and the Alper Research Center for Environmental Genomics of the University of California, Los Angeles Jonsson Comprehensive Cancer Center.

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Disclosure of Potential Conflicts of Interest: All authors declare they have no conflict of interests.

Word Count: 239 words in abstract; 2,942 words for body text

Number of References: 43

Total Number of Figures and Tables: 4 tables

Abstract

Protective effect of garlic on the development of cancer has been reported in *in vitro* and *in vivo* experimental studies. However, few human epidemiological 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. Epidemiological 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 employed to estimate adjusted odds ratios (OR) and their 95% confidence intervals (CIs), and to evaluate the ratio of odds ratios (ROR) for multiplicative interactions between raw garlic consumption and other risk factors. After adjusting for potential confounding factors, raw garlic consumption of ≥ 2 times per week is inversely associated with lung cancer (OR = 0.56, 95% CI = 0.44-0.72) with a monotonic dose–response relationship (*p* for 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 vapor from high-temperature cooking oil (ROR = 0.77, 95% CI = 0.59-1.00). In conclusion, intake of raw garlic is inversely associated with lung cancer with a dose-response pattern, suggesting that garlic is protective against lung cancer. The effective components in garlic in chemoprevention warrant further in-depth investigation.

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Introduction

Lung cancer is one of the most common causes of cancer death, with 1.4 million deaths (18.2% of the total cancer deaths) 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 a number of carcinogens that are known to induce lung cancer as demonstrated by numerous epidemiological studies and extensive basic scientific research (7). Specific lung carcinogens defined by the International Agency for Research on Cancer (IARC) include active smoke, environmental tobacco smoke, occupational exposures such as to asbestos crystalline silica, and ionizing radiation, air pollution, coal related pollution and indoor emissions from household combustion (8). Intake of fried food and inhaling of cooking oil vapor were suggested as risk factors for lung cancer, particularly among Chinese women (9, 10). While few protective factors have been identified for lung cancer, a meta-analysis based on a 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 used as both a spice and a medicine for thousands of years. It is widely consumed as a popular spice added to many edible preparations. The

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first documented application of garlic in traditional Chinese medicine could be traced back to 2000 BCE, when it was believed to possess miraculous properties for curing poisoning. Garlic was documented in Chinese Herbal Medicine Materia Medica (13-15). When bulb breaks up into separate cloves and its membrane disrupts, there are many volatile, lipid-soluble organo-sulfur compounds (OSCs) including allicin, diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS), that are responsible for the strong taste and smell (16). Many of the beneficial effects of garlic are attributed to high levels of OSCs (17, 18). The volatile oil containing OSCs can be excreted via the lungs, which may contribute to the potential protective effects for lung cancer. Both *in vitro* and *in vivo* experimental studies have suggested a protective effect by garlic and its components for cancer risk reduction in a variety of organ sites including the lung (19-25). However, few epidemiologic studies have been conducted to evaluate the relationship between garlic consumption and lung cancer risk (26-30). Based on data collected from a population-based case–control study with large sample size conducted in two counties of Jiangsu Province, China (31), we investigated the association of raw garlic consumption with lung cancer risk, 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

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data (32). Both 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 two 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 new patients diagnosed with primary lung cancer within 12 months, aged 18 years or older and have resided in the area for at least 5 years. 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 cancers including cancers of esophagus, stomach, and liver, we included controls for all four 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 cases and controls were recruited from 2003-2007 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

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This study was approved by the Institutional Review Board of Jiangsu Provincial Health Department. Written informed consent was obtained from each participants. 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. Population controls were interviewed twice a year. 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), family history of lung cancer or any other cancers and physical activity. Dietary data were collected using a modified version of a validated food frequency questionnaire (FFQ) in Han population (35, 36).

Statistical analysis

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Data were entered using Epidata 3.0 (EpiData Association, Denmark), cleaned and analyzed using SAS v9.2 package (SAS Institute, Inc., Cary, NC). 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 were 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. Chi-square 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% CIs 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 performed 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 re-coded 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 three measures of additive interaction – relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI) and their 95% CIs (38-40). If 95% CIs of the RERI and AP include 0 and that of SI includes 1, they are interpreted as no obvious additive interaction. Since there was no significant difference in the association between raw garlic consumption and lung cancer between the two counties, data from two counties were combined to increase the statistical power.

Based on 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 (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 socio-economics 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 with the exceptions of gender, mean age and body mass index (BMI).

The associations between risk or protective factors and lung cancer (ORs and 95% CIs) are presented in Table 2. Tobacco smoking (ever vs. never) was confirmed as a strong risk factor for lung cancer with adjusted ORs of 2.54 (95% CI = 2.17-2.99). A strong dose-response pattern was observed between pack-years of tobacco smoking and lung cancer (p for trend <0.0001). Environmental exposure to the possible pollution from factories nearby (adjusted OR = 1.55, 95% CI = 1.28-1.89), indoor exposure to the vapor from cooking oil (adjusted OR

= 1.26, 95% CI = 1.10-1.43), frequently consuming fried 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 in green tea drinking (adjusted OR = 0.85, 95% CI = 0.73-1.00) and physical exercise ten 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, ORs for consuming raw garlic < 2 times/week and ≥ 2 times/week were 0.92 (95% CI = 0.79-1.08) and 0.56 (95% CI = 0.44-0.72) respectively, compared to individuals who never ate raw garlic. A monotonic dose–response relationship was also observed (p for trend < 0.001). Similar inverse associations between raw garlic consumption and lung cancer were observed, when stratified by study area, the alcohol drinking status, factory nearby, exposure to vapor from cooking oil, intake of fried foods and poor ventilation in the kitchen. A stronger inverse association between lung cancer and raw garlic consumption was found among smokers, but only a borderline inverse association was observed among never smokers (adjusted OR = 0.67, 95% CI = 0.43-1.05).

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 (ROR = 0.78, 95% CI = 0.67-0.90). A

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multiplicative interaction was observed between raw garlic consumption and inhalation of vapor from 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, inhaling the vapor from high-temperature cooking oil and intake of fried foods were identified as risk factors for lung cancer. Additive and multiplicative interactions were observed between raw garlic consumption and these 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 <2 times/week or ≥2 times/week corresponded to an intake of raw garlic of 8.4g/week or 33.4 g/week, respectively. The association of the quantity of raw garlic consumed and lung cancer produced a similar pattern as that of raw garlic consumption frequency (data not shown). Information about garlic in the other spices was not included in the questionnaire since 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 and lung cancer was observed among never smokers, which is most likely explained by small sample size of non-smoking cases.

There has been only one recently published paper on the association between raw garlic consumption and lung cancer in Chinese population (26). The hospital-based study, including

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226 female lung cancer cases and 269 female healthy controls in Fujian Province, southern China, reported an inverse association between the 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 employed the same questionnaire designed for our study and was largely on female non-smokers (222 cases and 268 controls). It was not able to evaluate 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.

The protective effect of other forms of garlic consumption was observed epidemiologically on the development of cancers of colon, prostate, esophagus, larynx, oral cavity, ovary, and kidney (41). Nonetheless, results were inconsistent as to 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 supplements together with any other supplement use (n = 13 cases), compared to any other supplement use. However, lung cancer was found to be positively associated with exclusively garlic supplements use (n = 23 cases), compared to no supplements use (27). This positive association may be caused by small number of cases in the exposure categories and may be confounded by other factors (28). The European Prospective Investigation into Cancer and Nutrition (EPIC) reported protective effects of vegetables and fruit intakes 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).

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Protective effect of raw garlic consumption on lung cancer is supported by in *vitro* and animal experimental studies (21-25). Garlic and its related OSCs have been shown to influence genetic and epigenetic events involved with cancer. These include inhibiting mutagenesis, cell proliferation and tumor growth, blocking the carcinogen DNA adduct formation, scavenging free-radicals and modulating immune responses (42). These experimental evidences are supportive for the hypothesis that raw garlic consumption is protective against lung cancer.

Consistent with previous studies, tobacco smoking, air pollution and hereditary factors are risk factors of lung cancer. Exposure to vapor from high-temperature cooking oil, intake of fried foods and poor ventilation in the kitchen were found to be positively associated with lung cancer in current study. Consistent with our finding, green tea drinking and lung cancer, in a 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. In order to minimize selection bias, we adopted a population-based case-control study design. Cases were identified from the county tumor registry rather than from hospitals; while healthy controls were selected randomly from the same source population as cases. Because raw garlic consumption was not a known risk or protective factor for lung cancer, the differential recall bias might be limited. However, non-differential recall or interview bias may still exist, which might lead to underestimation of observed association towards to null, making our observed association conservative. In this study, we have a relatively low participation rate (46.3%) and a low proportion of pathological diagnosis (17%) among cases because most of cases are diagnosed at the advanced stage with no surgical treatment. This may lead to potential selection bias by including less severe lung cancer patients and makes the analysis by pathologic type of lung cancer impossible. BMI was calculated based on the measured weight and height at time of interview, which might result in 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 fried 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 factor of the difference between crude and adjusted ORs due to different garlic consumption patterns between two counties. In spite of potential limitations, the current study is population-based case-control study in a high risk population with a large sample size. The epidemiologic data were collected with a comprehensive questionnaire and a quality control procedure in place. The study evaluated both main associations with raw garlic consumption and potential interactions with other risk/protective factors.

In conclusion, inverse association between consumption of raw garlic and lung cancer has been observed in the present study with a clear dose-response pattern, suggesting that raw garlic is protective against lung cancer. The effective components in raw garlic that confer the prevention warrant further in-depth investigation.

Acknowledgements

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The authors thank the subjects for their voluntary participation as well as the staff of local Health Bureaus and local CDCs in Dafeng and Ganyu County for their assistance in the field work.

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Table 1. Demographic information and socio-economic status of cases and controls

Variables	Case (%) (N = 1,424)	Control (%) (N = 4,543)	*P*-value[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 (year)			
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
<1000	284(19.9)	959(21.1)	
1000-	266(18.7)	843(18.6)	
1500-	380(26.7)	1,234(27.2)	
≥2500	494(34.7)	1,507(33.2)	0.670
Body mass index (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]Based on Chi-square testing; T-testing for the mean. [b]Chinese recommend standard was used for the cut-off points of overweight and obesity: low weight (BMI < 18.5), overweight (BMI≥24.0 and BMI < 28.0), obesity (BMI≥28.0).

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

Variables	Case (%) (N = 1424)	Control (%) (N = 4543)	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 years	262(18.4)	1,088(23.9)	1.14(0.96-1.35)	1.60(1.32-1.94)
≥30 years	768(53.9)	1,595(35.1)	2.27(1.98-2.61)	3.68(3.08-4.40)
p for 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	651(264.6)	2,539(619.3)	1.00	1.00
Yes	773(314.2)	2,004(488.8)	1.33(1.18-1.51)	1.26(1.10-1.43)
Intake of fried foods				
No	926(65.0)	3,382(74.4)	1.00	1.00
Yes	498(35.0)	1,161(25.6)	1.50(1.34-1.70)	1.32(1.15-1.52)
Poor ventilation in kitchen				
No	537(38.3)	1,925(42.6)	1.00	1.00
Yes	866(61.7)	2,599(57.4)	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), body mass index (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 3. The association between lung cancer and raw garlic consumption frequency stratified by major factors

Stratification variables	Never [a]	<2times/week		≥2times/week		*p* for trend [b]
	Case/ Control	Case/ Control	Adjusted OR(95% CI)[b]	Case/ Control	Adjusted OR(95% CI)[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 years	129/575	119/416	0.97(0.69-1.36)	14/97	0.42(0.22-0.80)	0.046
≥30 years	212/14	381/753	0.86(0.69-1.08)	310/630	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
Intake of fried foods						
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 ten 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), body mass index (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).

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 years	No	381/753	1.00	1.00
≥30 years	Yes[b]	387/842	0.91(0.77-1.08)	0.68(0.56-0.83)
<30 years	No	129/575	0.44(0.35-0.56)	0.38(0.30-0.48)
<30 years	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)		
Intake of fried foods				
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), body mass index (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.

Author Manuscript Published OnlineFirst on May 8, 2013; DOI: 10.1158/1940-6207.CAPR-13-0015
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

American Association for Cancer Research

Cancer Prevention Research

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Cancer Prev Res Published OnlineFirst May 8, 2013.