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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 *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 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 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.

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Keywords

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

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 mortality 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 smoking is a well-established group I carcinogen for lung cancer by numerous epidemiological studies and with extensive basic scientific research (7). Specific lung carcinogens defined by International Agency for Research on Cancer (IARC) 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). While 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 herb 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 Chinese traditional medicine could be traced back to 2000 BCE, when it was believed to 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 organo-sulfur compounds (OSCs) in the volatile oil, including allicin, diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS) (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). 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, 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 later 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 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 adult lung cancer patients, 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 prior to 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 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 our subjects 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

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, 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 (FFQ) 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, 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 between complete data when missing was excluded and data with imputation. If the point estimates are equivalent, we present results from imputed data for the specific variable, otherwise, we

present results from complete data 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 to be 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.

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), incomes (Yuans/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, excepting 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 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 for 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 with 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, OR for eating raw garlic < 2 times/week and 2 times/week was 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 with raw garlic consumption 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 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 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 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 < 2 times/week or ≥ 2 times/week corresponded to an intake of raw garlic of 8.4g/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 frequency (data not shown). Information on 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 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 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 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.

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 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 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 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).

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 chemopreventive effects of garlic and related OSCs, including inhibition of mutagenesis by inhibiting the metabolism, inhibition of DNA adduct formation, free-radical scavenging, and effects on cell proliferation and tumor growth (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 PAHs. 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. In order to minimize selection bias, we adopted a population-based case-control study design. Cases were identified from the tumor registry data rather than from hospitals; while healthy controls were selected randomly from the same source population as the cases. Because raw garlic consumption is not a known risk or protective factor for lung cancer, the differential recall bias can 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 an advanced stage without 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 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. In spite of 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 the data collection has had 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 this 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.

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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
Incomes 10 years ago (Yuans/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

^aBased on Chi-square testing; T-testing for the mean.

^bChinese 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)
<i>p</i> 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)
Frying 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), incomes (Yuans/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 ^d		<2times/week		2times/week		p for trend ^b
	Case/Control	Adjusted OR(95% CI) ^b	Case/Control	Adjusted OR(95% CI) ^b	Case/Control	Adjusted OR(95% CI) ^b	
All raw garlic	704/2,423	0.92(0.79-1.08)	126/483	0.56(0.44-0.72)			<0.001
Study area							
Dafeng	515/1,954	0.71(0.56-0.92)	9/59	0.43(0.20-0.91)			0.001
Ganyu	189/469	1.15(0.94-1.42)	117/424	0.66(0.50-0.88)			0.013
Tobacco smoking							
Never smoker	194/1,095	0.95(0.72-1.26)	35/174	0.67(0.43-1.05)			0.137
All smokers	510/1,328	0.87(0.73-1.05)	91/309	0.56(0.42-0.74)			0.000
<30 years	129/575	0.97(0.69-1.36)	14/97	0.42(0.22-0.80)			0.046
30 years	212/14	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	0.98(0.80-1.19)	67/270	0.59(0.42-0.81)			0.010
Often	277/851	0.86(0.67-1.10)	59/213	0.56(0.38-0.82)			0.005
Factory nearby							
No	571/2,076	0.98(0.83-1.16)	112/448	0.60(0.46-0.78)			0.002
Yes	120/301	0.73(0.45-1.17)	13/28	0.37(0.16-0.89)			0.024
High-temperature cooking oil							
No	420/1,687	1.02(0.84-1.24)	81/338	0.57(0.41-0.78)			0.006
Yes	284/736	0.80(0.62-1.03)	45/145	0.57(0.38-0.85)			0.004
Frying foods							
No	455/1,714	0.81(0.65-1.02)	33/153	0.64(0.41-0.98)			0.016
Yes	249/709	0.92(0.74-1.14)	93/330	0.49(0.36-0.67)			<0.001
Poor ventilation in kitchen							
No	288/1,080	0.92(0.72-1.18)	48/205	0.52(0.35-0.78)			0.007
Yes	416/1,343	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	0.92(0.79-1.08)	123/477	0.57(0.44-0.73)			<0.001

Stratification variables	Never ^a		<2times/week		2times/week		p for trend ^b
	Case/Control	43/80	Case/Control	Adjusted OR(95% CI) ^b	Case/Control	Adjusted OR(95% CI) ^b	
Yes		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

^aThe reference group.

^b Adjusted on age (continuous), gender (male = 1, female = 0), education level (illiteracy = 1, primary = 2, middle = 3, high = 4, college = 5), incomes (Yuans/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 (Datfeng = 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)
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)
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)				
Frying 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)
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)				

^aAdjusted on age (continuous), gender (male = 1, female = 0), education level (illiteracy = 1, primary = 2, middle = 3, high = 4, college = 5), incomes (Yuans/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).

^bThe joint effects category for further estimation of additive interaction.

^cThe reference category for measures of interaction on additive scale.