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Consumption of garlic and its interactions with tobacco smoking and alcohol drinking on esophageal cancer in a Chinese population

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Abstract

Garlic consumption has been inversely associated with esophageal cancer (EC), however, its interactions with tobacco smoking and alcohol consumption have never been evaluated in an epidemiological study. We evaluated the potential interactions between garlic intake and tobacco smoking as well as alcohol consumption in a population-based case-control study with 2,969 incident EC cases and 8,019 healthy controls. Epidemiologic data were collected by face-to-face interview using a questionnaire. The adjusted odds ratio (OR) and 95% confidence interval (CI) were estimated and additive and multiplicative interactions were evaluated using unconditional logistic regression models, adjusting for potential confounding factors. Semi-Bayes (SB)

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adjustments were used to reduce potential false-positive findings. EC was inversely associated with raw garlic intake (SB-adjusted OR for more than once a week = 0.68, 95% CI: 0.57–0.80) with a strong dose-response pattern in the overall analysis and in the stratified analyses by smoking and drinking. EC was positively associated with smoking and alcohol drinking with SB-adjusted OR of 1.73 (95% CI: 1.62–1.85) and 1.37 (95% CI: 1.28–1.46) in dose-response effects of increased intensity and longer duration of smoking/drinking. Moreover, garlic intake interacts with smoking [synergy index (S) = 0.83, 95% CI: 0.67–1.02; Ratio of ORs (ROR) = 0.88, 95% CI: 0.80–0.98] and alcohol drinking (S = 0.73, 95% CI: 0.57–0.93; ROR = 0.86, 95% CI: 0.77–0.95) both multiplicatively and additively. Our findings suggested that high intake of raw garlic may reduce EC risk and may interact with tobacco smoking and alcohol consumption which might shed a light on the development of EC as well as potential dietary intervention among high risk smokers and drinkers for EC prevention in Chinese population.

Keywords

esophageal cancer; smoking; alcohol drinking; garlic; interaction; China

Introduction

Esophageal cancer (EC) is the eighth most frequently diagnosed cancer and sixth leading cause of cancer-related death worldwide with an estimated 455,800 new cases and 400,200 deaths, respectively (Ferlay *et al.*, 2015, Torre *et al.*, 2015). The incidence varies by region, with about 80% of patients worldwide occurring in less developed countries. China is among the countries with the highest EC incidence rate and mortality worldwide and accounts for about half of all EC patients and deaths, where an estimated 223,000 new cases and 197,000 deaths were reported in 2012 (Ferlay *et al.*, 2015, Torre *et al.*, 2015). Esophageal adenocarcinoma (EAC) has slowly replaced esophageal squamous cell carcinoma (ESCC) as the predominant type of EC in Western counties, while ESCC remains the most common histological type in China, representing 94.2% of total cases in China (Arnold *et al.*, 2015). For EC, the overall ratio of mortality to incidence is 0.88 and the geographical patterns in incidence and mortality are quite similar (Ferlay *et al.*, 2015, Torre *et al.*, 2015). Given the very poor prognosis, to identify potential protective factors for primary prevention is of great importance.

Epidemiology studies have extensively explored risk factors and protective factors for both histological types of EC. Tobacco smoking and alcohol drinking are the major risk factors consistently observed for both types, but many risk factors seem relevant to either cell type of cancer (Hongo *et al.*, 2009). Whereas gastroesophageal reflux disease, Barrett's esophagus, and obesity are associated with increased risk of EAC observed in developed countries. In comparison, poverty, low education level, achalasia, physical injury and intake of hot beverages are associated with risk of ESCC commonly seen in developing countries (Enzinger *et al.*, 2003, Hongo *et al.*, 2009, Maret-Ouda *et al.*, 2016). A few studies suggested inverse associations of physical activity, poultry and fish consumption, green tea drinking, and fruit and vegetables consumption with risk of EC. However the results of these potential factors remain inconclusive, especially for allium vegetables (Singh *et al.*, 2014, Yu *et al.*, 2014, Zhu *et al.*, 2014, Jiang *et al.*, 2016, Zheng *et al.*, 2013, Riboli *et al.*, 2003). Garlic (*Allium sativum*) is one of the most widely used of allium vegetables worldwide, and especially in China. *In vitro* and animal experimental studies have shown that allium vegetables and their bioactive substances have the protective effects against several types of cancers, including EC (Herman-Antosiewicz *et al.*, 2004, Milner, 2001, Yin *et al.*, 2014, Yu *et al.*, 2005), but this relationship so far has been rarely studied yielding inconsistent results among epidemiologic studies (Guercio *et al.*, 2016).

Although the joint effects tobacco smoking and alcohol drinking on EC risk have been reported, interactions of smoking and alcohol drinking with other factors, especially protective factors, on the development of EC are unclear (Steevens *et al.*, 2010, Wu *et al.*, 2011b, Prabhu *et al.*, 2014). Moreover, studies on garlic consumption published to date have been under powered for analyses of interactions and stratification (Guercio *et al.*, 2016). It is a question of whether raw garlic is a protective factor and may reduce the risk of EC for smoking, alcohol drinking, and combined smoking and drinking. To address the questions described above, we analyzed data collected from Jiangsu Four Cancers (JFC) Study, a large population-based case-control study conducted in four counties of Jiangsu province, China (Zhao *et al.*, 2017). We aimed to examine the independent associations of tobacco smoking, alcohol drinking, and raw garlic intake with the risk of EC. In addition, the joint effects among these 3 factors were evaluated on both multiplication and additive models.

Materials and Methods

Study design and participants

The detailed study design of the JFC Study has been described previously (Zhao *et al.*, 2017). To summarize, the JFC Study is a large-scale, population-based case-control study of the four most common cancers in China including the lung, liver, stomach, and esophageal from 2003 to 2010. Participants were identified from four counties in Jiangsu, Southeastern province in China with an estimated age-adjusted mortality rate of 20.2 per 100,000 for EC in 2012 (Zhou *et al.*, 2012). The four counties of Dafeng, Ganyu, Chuzhou, and Tongshan, cover a population of about 4.3 million and have well-established population-based cancer registries, operated by county center for disease control and prevention (CDC).

Cases were patients aged at least 18 years, residents at least 5 years as local residents of the respective county, and newly registered primary cases in local cancer registries (within 1 year). Healthy controls were identified from a demographic database of each county. Eligible controls had the same inclusion criteria with cases but were without any diagnosis or history of any cancer. For each case of EC, controls were randomly selected and matched by gender and age (±5 years) and county. To increase statistical power in this study, all healthy controls, including those for other three cancers, are included in the analysis, resulting in a total of 2,969 cases and 8,019 controls.

Data collection

The JFC Study protocol was approved by the Institutional Review Board of Jiangsu Provincial Health Department and the Human Subject Protection Committee University of

California, Los Angeles (UCLA). Written informed consent was provided by all participants before entering the study.

A structured questionnaire was designed to collect relevant data and had been previously tested (Mu *et al.*, 2005). Face-to-face interviews with all participants were administered by trained public health professionals at the county CDC. The questionnaire included demographic and socioeconomic factors, residential environment, dietary history, lifestyle information such as tobacco smoking and alcohol drinking, and personal and family medical history. We collected details of smoking and alcohol drinking habits, including age at starting smoking/drinking, years of consumption, cigarettes per day, weekly frequency of drinking, and the amount of different types of alcohol beverages drinking (e.g., beer, wine, and liquor). Dietary intake was assessed by a Food Frequency Questionnaire (FFQ) on 90 food items. We assessed each subject's total energy intake by summing the energy of each food item consumption together based on the Chinese Food Composition Tables (Yang *et al.*, 2009). Of particular interest, raw garlic consumption was evaluated by asking "Do you eat raw garlic every week?" Three responses were possible: never, < 2 times/week, and ≥ 2 times/week.

Statistical analysis

Descriptive analyses based on the Chi-square test were performed for the distribution differences of demographic characteristics (sex, age, education level, income 10 years ago), body mass index (BMI), tobacco smoking, alcohol drinking, family history of EC, and county of residence between cases and controls. Unconditional logistic regression analyses were used to estimate the effects of raw garlic consumption on EC risk. Both crude and adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI) were computed. Moreover, OR for each exposure category and p value for linear trend across levels of exposure were calculated in a logistic regression model, using dummy coding and ordinal coding.

Multiplicative and additive interactions were estimated among tobacco smoking, alcohol drinking, and raw garlic consumption on EC risk. Ratio of ORs (ROR) was examined for multiplicative interaction by including main effect variables and their product terms in a logistic regression model. Three measures of the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S) were assessed for additive interaction (Andersson *et al.*, 2005, Knol *et al.*, 2007). In the absence of an additive effect, RERI and AP both equal 0 and S equal 1. We employed the semi-Bayes (SB) method to report posterior estimates that incorporate associations from observed data with null prior associations (Prior OR = 1.00, 95% CI: 0.25–4.00) to reduce false -positive findings in our study (Greenland, 2007).

Based on prior knowledge and confounding assessment, we selected the following covariates in the multivariate analysis model: sex (male = 1, female = 0), age (continuous), education level (illiteracy = 1, primary = 2, middle = 3, high or college = 4), income 10 years ago (Yuan/year, continuous), body mass index (continuous), family history of esophagus cancer (yes = 1, no = 0), county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4), pack-year of smoking (continuous), ethanol consumption in 1990s (ml/week, continuous), and total energy intake (kcal/month, continuous).

We double entered data into Epidata 3.0 (EpiData Association, Denmark). SAS v9.2 (SAS Institute, Inc., Cary, NC, USA) was used for data cleaning and analyses.

Results

Table 1 shows the distribution of demographics of participants between EC cases and controls. With the exception of gender, there were significant differences between cases and controls in the county of residence, age, education levels, incomes 10 years ago, body mass index (BMI), and family history of EC ($P < 0.001$).

Table 2 displays the associations between tobacco smoking-related variables and EC. Compared to never smokers, ever, former and current smoking are associated with EC with SB-adjusted OR of 1.73 (95% CI: 1.62–1.85), 1.61 (95% CI: 1.44–1.80) and 1.32 (95% CI: 1.23–1.41), respectively. Positive associations with dose-response relationships were observed between smoking-related variables and EC including age at starting smoking, years of smoking, cigarettes per day and pack-years of smoking (P_{trend} for each variable < 0.001)

The associations for EC risk with major alcohol drinking variables are presented in Table 3. Compared to never alcohol drinking, ever drinking was associated with EC with SB-adjusted OR of 1.37 (95% CI: 1.28–1.46). The SB-adjusted ORs for former drinking and current drinking were 1.61(95% CI: 1.44–1.80) and 1.32(95% CI: 1.23–1.41), respectively. Positive associations with dose-response relationships were significantly observed between EC and alcohol-related variables including alcohol drinking frequency, age at starting drinking, years of drinking, and ethanol consumption in 1990s (P_{trend} for each variable < 0.001).

Table 4 presents the overall association between raw garlic consumption and EC and stratified associations by county, sex, ever smoking, and alcohol drinking. Compared with never consumption, SB-adjusted OR for eating raw garlic < 2 times/week and ≥ 2 times/week was 0.99 (95% CI: 0.89–1.11) and 0.68 (95% CI: 0.57–0.80), respectively and a strong dose-response pattern was observed between increased consumption of raw garlic and EC risk ($P_{trend} < 0.001$). After adjusting for confounding factors and semi-Bayes adjustment, the inverse association between raw garlic consumption ≥ 2 times/week and EC with a monotonic dose-response pattern observed consistently across all strata, except for county. Consistent associations were observed in stratified analyses among non-smokers and non-drinkers.

The joint effects of smoking, alcohol drinking, and raw garlic consumption on esophageal cancer risk are shown in Table 5. After adjusting for confounding factors, interactions were observed between raw garlic consumption and alcohol drinking frequency (ROR = 0.86, 95% CI: 0.77–0.95; S = 0.73, 95% CI: 0.57–0.93) and between raw garlic consumption and tobacco smoking (ROR = 0.88, 95% CI: 0.80–0.98), and borderline significantly on an additive scale (S = 0.83, 95% CI: 0.67–1.02). As expected, we observed interactions between pack-years of smoking and alcohol drinking frequency (ROR = 1.11, 95% CI: 1.04–1.18; S = 1.54, 95% CI: 1.13–2.08).

Table 6 describes additional analyses of the joint effects of garlic intake with both tobacco smoking and alcohol drinking. Individuals with low consumption of raw garlic (never and less than twice a week), nondrinkers and nonsmokers were grouped as a reference group. After adjusting for confounding factors, high intake of garlic was inversely associated with ES among non-smokers and non-drinkers, only smokers, only drinkers, as well as individuals who were both smoking and drinking.

Discussion

In this large population-based case-control study, we confirmed tobacco smoking and alcohol drinking are strongly associated with EC, with dose-response patterns. Increased consumption of raw garlic was inversely associated with EC among overall population as well as in the stratified analyses by tobacco smoking and alcohol drinking. Additive and multiplicative interactions were observed between smoking and alcohol drinking on EC. Moreover, both multiplicative and additive interactions were observed between raw garlic consumption and tobacco smoking and alcohol drinking. Compared to the reference group of low consumption of raw garlic, nondrinking and nonsmoking, consuming raw garlic twice or more a week were inversely associated with EC for smoking only, alcohol drinking only, and individuals who were both smokers and alcohol drinkers.

Tobacco smoking and alcohol drinking are considered as important risk factors for EC, which are responsible for about 31.4% and more than 90% of EC occurrence in China and Western countries, respectively (Castellsagué *et al.*, 1999, Wu *et al.*, 2011a). However, the magnitude of the association might be varied by different factors, including intensity and duration of smoking/drinking, race and regions (Castro *et al.*, 2017, Prabhu *et al.*, 2013). A meta-analysis indicated that compared with never smokers, the pooled adjusted ORs of tobacco smoking with ESCC risk were 2.31 for current, 2.52 for more than 20 cigarettes daily, and 2.34 for more than 20 years in Asia, which were slightly higher than ORs observed in our study (Prabhu *et al.*, 2013). However, the association of tobacco smoking with ESCC risk in Asia seemed to weaker than in South American (OR = 3.29, 95% CI: 1.75– 6.18) and Europe (OR = 4.21, 95% CI: 3.13–5.66) when comparing current with never smokers, as well as ORs for number cigarettes daily and years of smoking (Prabhu *et al.*, 2013). For ever alcohol drinking, the adjusted OR of 1.40 in our study was slightly lower than the pooled OR of 1.78 (95% CI: 1.38–2.30) for EC among Chinese population, but slightly higher the pooled OR of 1.21 in Asian population (Li *et al.*, 2011, Prabhu *et al.*, 2014). The association of alcohol drinking with EC risk also seemed to be stronger in Western populations with OR of 4.03 in men and 1.42 in women (Castellsague *et al.*, 1999). Moreover, consistent with previous studies among Western population, we also observed strong dose-response relationships between smoking/alcohol-related variables and EC including increased intensity and longer duration of smoking/drinking (Castellsague *et al.*, 1999, Zambon *et al.*, 2000).

To our knowledge, this is the largest study to explore the effect of raw garlic on EC globally. Up to the time this manuscript was written, 14 case-control studies and 2 cohort studies reported associations between allium vegetables and EC risk, with 9 studies conducted in the Chinese population (Galeone *et al.*, 2006, Kim *et al.*, 2009, Guercio *et al.*, 2016). Our findings are consistent with a recent meta-analysis where pooled RRs of ESCC were 0.68 (95% CI: 0.50–0.92) for highest versus the lowest category of garlic consumption based on 8 studies (Guercio *et al.*, 2016). Five studies in line with our study reported significant inverse association of garlic consumption with EC risk among the Chinese population, while 4 studies found it insignificant (Guercio *et al.*, 2016). All studies conducted in Western population reported insignificant inverse association, except that only 1 case-control study reported that the highest category of garlic and onion intake reduce the risk of EC (Galeone *et al.*, 2006, Kim *et al.*, 2009, Guercio *et al.*, 2016). This may be because of lower intake in Western countries or reflect the difference in protective effects of garlic on EC risk between the Chinese and Western populations. Moreover, most of previous studies were based on small numbers and were under-powered for stratified analyses and interaction assessment.

This is the first time, interactions were observed between raw garlic consumption and tobacco smoking as well as alcohol drinking on both multiplicative and additive scales. Many studies have examined the joint effects of tobacco smoking with alcohol drinking on EC risk (Steevens *et al.*, 2010, Wu *et al.*, 2011b, Prabhu *et al.*, 2014). A meta-analysis indicated the use of both tobacco and alcohol was associated with a 3.28-folds risk for ESCC compared with nonuse. The joint effect of both risk factors was observed strongly among Western population, as the EC risk was increased 8-folds in ever users, and even 130 folds in the highest joint level of smoking and alcohol drinking (Castellsague *et al.*, 1999, Zambon *et al.*, 2000). Consistent with previous studies, we observed multiplicative and additive interactions between tobacco smoking and alcohol drinking on the development of EC. There have been no studies so far evaluated the interactions of garlic consumption with both major risk factors. Hence, the present study provides a new evidence for the interactions and joint effects of garlic intake with both tobacco smoking and alcohol drinking on EC.

The general mechanisms of carcinogenesis by tobacco and alcohol are due to their many carcinogens such as acetaldehyde in the metabolism of ethanol, polycyclic aromatic hydrocarbons and N-nitrosamines in smoke. Those carcinogens can interact with DNA to form stable DNA adducts, leading to permanent gene mutations (Toh *et al.*, 2010). The beneficial effects of raw garlic are believed to be mainly attributable to their rich sources of organosulfur compounds and flavonoids (Le *et al.*, 2000). Several molecular mechanisms have been proposed to explain the anticancer effects of garlic and related compounds. These include (1) inhibition of cancer initiation via inhibition of activation of carcinogens, modulation of carcinogen metabolism, inhibiting the formation of DNA adducts with carcinogens, as well as stimulation of glutathione (GSH) synthesis; (2) blocking cancer promotion through controlling cell proliferation, inhibition of cell-cycle progression, and induction of apoptosis; (3) scavenging of free radicals; (4) histone modification, and (5) inhibition of angiogenesis (Bianchini *et al.*, 2001, Le, 2002, Omar *et al.*, 2010, Herman-Antosiewicz *et al.*, 2004, Sengupta *et al.*, 2004, Powolny *et al.*, 2008, Nicastro *et al.*, 2015). The esophagus is directly exposed to the effective compounds upon consumption of garlic as well as the consistent absorption of the volatile oil released in the stomach. Also, garlic and related compounds may act through the mechanisms described above to protect against EC risk caused by smoking and alcohol drinking.

Several limitations and biases were present in this study. First, a cause-and-effect relationship between raw garlic consumption and EC risk cannot be established due to the nature of retrospective design. Second, selection bias may affect the observed association. Most of the patients were diagnosed at an advanced stage without surgical treatment, the participation rates were 87% among controls and 30% among EC cases, and proportion of pathologic diagnosis was 41.8% among cases, participants in our study might not include severe EC patients. The observed associations might not be generalizable to EC advanced patients. On the other hand, the selection bias might probably be minimized, because of population-based study design (Chen *et al.*, 2017, Buczko, 1994). Third, information bias and recall bias may exist in our study. Self-reported data without accurate measurements is likely to lead to some misclassification of tobacco smoking, alcohol dinking, and raw garlic intake between cases and controls. However, study participants did not know any potential link between garlic intake and EC risk, which would most likely lead to non-differential bias towards to null, making our observed association conservative. On the other hand, cases might quit smoking and drinking because of early digestive symptoms, leading to a weaken association and an inflated association among former users. Fourth, sensitivity analysis was carried out for potential confounding factors. County of residence rather than smoking, drinking, dietary factors such as fruit, vegetables, meat and total energy drove the difference between crude and adjusted ORs due to differing garlic consumption patterns. Analogous findings were also reported among lung cancer patients in previous studies (Jin *et al.*, 2013, Myneni *et al.*, 2016). Thus, the protective effect role of raw garlic consumption may differ by geographic region. Despite the above limitations, there are a number of unique strengths of current study, including: (1) it was population-based study; (2) the study has the largest sample size among Chinese population; (3) comprehensive analyses can be conducted and detailed information on various risk factors including tobacco smoking and alcohol drinking of EC were collected; (4) has the ability to perform stratified analysis and to evaluate potential interactions of raw garlic intake with smoking and alcohol drinking on EC risk.

In conclusion, our study provides further evidence for the protective effect of raw garlic consumption against EC and suggests the risk of esophageal cancer among smokers and alcohol drinkers could be modified by raw garlic consumption. The consumption of raw garlic may be recommended in the regular diet for esophageal cancer prevention among Chinese population, together with tobacco cessation and alcohol reduction.

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Novelty and Impact

Garlic consumption has been inversely associated with esophageal cancer (EC), however, its interactions with tobacco smoking and alcohol consumption have never been evaluated in an epidemiological study with large sample size. We conducted this population-based case-control study to assess joint effects and interactions of garlic intake with tobacco smoking and alcohol drinking on EC. We observed raw garlic intake is a protective factor for EC and interacts with smoking and drinking. This is the first time that we report interactions between garlic intake and tobacco smoking as well as alcohol consumption on both multiplicative and additive scales. Our observations suggest that in addition to tobacco cessation and alcohol reduction, garlic intake should also be included as one of the prevention strategy for EC in Chinese population.

Table 1

Characteristics of participants by status of cases and controls

Variables	Case (N=2,969, %)	Control (N=8,019, %)	P^a
County of residence			<0.001
Dafeng	639(21.5)	2,536(31.6)	
Ganyu	931(31.4)	2,010(25.1)	
Chouzhou	968(32.6)	1,180(14.7)	
Tongshan	431(14.5)	2,293(28.6)	
Sex			0.2627
Male	2,103(70.8)	5,767(71.9)	
Female	866(29.2)	2,252(28.1)	
Age (years)			<0.001
<50	138(4.6)	884(11.0)	
50-	668(22.5)	1,794(22.4)	
60-	1,095(36.9)	2,565(32.0)	
≥70	1,068(36.0)	2,776(34.6)	
Education level			<0.001
Illiteracy	1,723(58.0)	3,839(47.9)	
Primary	900(30.3)	2,525(31.5)	
Middle	289(9.7)	1,320(16.5)	
High or college	57(1.9)	335(4.2)	
Income 10 years ago (Yuan/year)			<0.001
<1000	887(29.9)	1,718(21.4)	
1000-	641(21.6)	1,555(19.4)	
1500-	793(26.7)	2,146(26.8)	
≥2500	648(21.8)	2,600(32.4)	
Body mass index (BMI)[b]			<0.001
<18.5	468(15.8)	455(5.7)	
18.5–23.9	1,973(66.5)	4,875(60.8)	
24.0–27.9	425(14.3)	2,234(27.9)	
≥28.0	103(3.5)	455(5.7)	
Family history of esophagus cancer			<0.001
No	2,435(82.0)	7,342(91.6)	
Yes	534(18.0)	677(8.4)	

[a] Chi-square test for difference distribution between cases and controls.

[b] Chinese recommend standard was used for the cutoff points of overweight and obesity.

Table 2

The associations between tobacco smoking and esophageal cancer

Variables	Case (N=2,969, %)	Control (N=8,019, %)	Crude OR (95%CI)	Adjusted OR (95%CI)[a]	SB-Adjusted OR (95%CI)[a]
Smoking status					
Never	1,159(39.0)	4,292(53.5)	1.00	1.00	1.00
Ever	1,810(61.0)	3,727(46.5)	1.80(1.65–1.96)	1.63(1.46–1.81)	1.73(1.62–1.85)
Former	599(20.2)	850(10.6)	2.61(2.31–2.95)	2.73(2.36–3.16)	2.66(2.42–2.92)
Current	1,211(40.8)	2,877(35.9)	1.56(1.42–1.71)	1.35(1.20–1.51)	1.47(1.37–1.58)
Pack-years of smoking					
Never smoker	1,159(39.0)	4,292(53.5)	1.00	1.00	1.00
<30 years	613(20.6)	1,514(18.9)	1.50(1.34–1.68)	1.45(1.27–1.65)	1.48(1.36–1.61)
≥30 years	1,197(40.3)	2,213(27.6)	2.00(1.82–2.20)	1.78(1.58–2.01)	1.91(1.77–2.06)
P_{trend}			<0.001	<0.001	
Age at starting smoking					
Never	1,159(39.0)	4,292(53.5)	1.00	1.00	1.00
≥30 years	372(12.5)	726(9.1)	1.90(1.65–2.18)	1.50(1.28–1.76)	1.71(1.54–1.90)
20–30 years	1,106(37.3)	2,224(27.7)	1.84(1.67–2.03)	1.70(1.51–1.91)	1.78(1.65–1.92)
<20 years	332(11.2)	777(9.7)	1.58(1.37–1.83)	1.58(1.33–1.87)	1.58(1.42–1.76)
P_{trend}			<0.001	<0.001	
Years of smoking					
Never	1,159(39.0)	4,292(53.5)	1.00	1.00	1.00
<30 years	316(10.6)	837(10.4)	1.40(1.21–1.62)	1.45(1.23–1.71)	1.42(1.27–1.58)
30–40 years	608(20.5)	1,130(14.1)	1.99(1.77–2.24)	1.78(1.55–2.04)	1.90(1.74–2.08)
≥40 years	886(29.8)	1,760(21.9)	1.86(1.68–2.07)	1.61(1.41–1.83)	1.76(1.62–1.91)
P_{trend}			<0.001	<0.001	
Cigarettes per day					
Never	1,159(39.0)	4,292(53.5)	1.00	1.00	1.00
<20 cig/day	656(22.1)	1,467(18.3)	1.66(1.48–1.85)	1.48(1.30–1.69)	1.58(1.45–1.72)
≥20 cig/day	1,154(38.9)	2,260(28.2)	1.89(1.72–2.08)	1.74(1.55–1.97)	1.83(1.70–1.97)
P_{trend}			<0.001	<0.001	

[a]Adjusted for sex (male = 1, female = 0), age (continuous), education level (illiteracy = 1, primary = 2, middle = 3, high or college = 4), income 10 years ago (Yuan/year, continuous), body mass index (continuous), family history of esophagus cancer (yes = 1, no = 0), county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4), and ethanol consumption in 1990s (ml/week, continuous).

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Table 3

The associations between alcohol consumption and esophageal cancer

Variables	Case (N=2,969, %)	Control (N=8,019, %)	Crude OR (95%CI)	Adjusted OR (95%CI)[a]	SB-Adjusted OR (95%CI)[a]
Drinking status					
Never	1,372(46.2)	4,303(53.7)	1.00	1.00	1.00
Ever	1,597(53.8)	3,716(46.3)	1.35(1.24–1.47)	1.40(1.26–1.56)	1.37(1.28–1.46)
Former	314(10.6)	618(7.7)	1.59(1.37–1.85)	1.63(1.38–1.92)	1.61(1.44–1.80)
Current	1,283(43.2)	3,098(38.6)	1.30(1.19–1.42)	1.35(1.20–1.51)	1.32(1.23–1.41)
Alcohol drinking frequency					
Never	1,372(46.2)	4,303(53.7)	1.00	1.00	1.00
Occasionally	546(18.4)	1,472(18.4)	1.16(1.04–1.31)	1.25(1.10–1.43)	1.20(1.10–1.31)
Often	1,051(35.4)	2,244(28.0)	1.47(1.34–1.62)	1.52(1.35–1.72)	1.49(1.38–1.60)
P_{trend}			<0.001	<0.001	
Age at starting drinking					
Never	1,372(46.2)	4,303(53.7)	1.00	1.00	1.00
≥30 years	580(19.5)	1,321(16.5)	1.38(1.23–1.55)	1.34(1.17–1.53)	1.36(1.25–1.48)
20–30 years	863(29.1)	1,993(24.9)	1.36(1.23–1.50)	1.45(1.28–1.64)	1.39(1.29–1.51)
<20 years	154(5.2)	402(5.0)	1.20(0.99–1.46)	1.39(1.12–1.74)	1.28(1.11–1.48)
P_{trend}			<0.001	<0.001	
Years of drinking					
Never	1,372(46.2)	4,303(53.7)	1.00	1.00	1.00
<30 years	471(15.9)	1,307(16.3)	1.13(1.00–1.28)	1.31(1.13–1.52)	1.20(1.09–1.32)
30–40 years	477(16.1)	983(12.3)	1.52(1.34–1.73)	1.62(1.40–1.88)	1.56(1.42–1.72)
≥40 years	649(21.9)	1,426(17.8)	1.43(1.28–1.60)	1.33(1.16–1.53)	1.39(1.27–1.51)
P_{trend}			<0.001	<0.001	
Ethanol consumption in 1990s					
Never	1,642(55.3)	5,062(63.1)	1.00	1.00	1.00
<500 ml/week	547(18.4)	1,457(18.2)	1.16(1.03–1.30)	1.16(1.02–1.32)	1.16(1.07–1.26)
≥500 ml/week	780(26.3)	1,500(18.7)	1.60(1.45–1.78)	1.55(1.36–1.76)	1.58(1.46–1.71)
P_{trend}			<0.001	<0.001	

[a]Adjusted for sex (male = 1, female = 0), age (continuous), education level (illiteracy = 1, primary = 2, middle = 3, high or college = 4), income 10 years ago (Yuan/year, continuous), body mass index (continuous), family history of esophagus cancer (yes = 1, no = 0), county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4), and pack-year of smoking (continuous).

Table 4

Raw garlic consumption associated with esophageal cancer stratified by selected factors

Stratification variables	Never	<2times/week			≥2times/week			p_{trend}[a]
	Case/ Control	Case/ Control	Adjusted OR (95% CI)[a]	SB-Adjusted OR (95% CI)[a]	Case/ Control	Adjusted OR (95% CI)[a]	SB-Adjusted OR (95% CI)[a]	
All participants								
All raw garlic	1,505/3,709	1,183/3,076	0.99(0.89–1.11)	0.99(0.89–1.11)	281/1,234	**0.67(0.57–0.80)**	**0.68(0.57–0.80)**	**<0.001**
County of residence								
Dafeng	528/1,957	101/520	0.81(0.64–1.04)	0.82(0.64–1.04)	10/59	0.65(0.32–1.31)	0.71(0.38–1.33)	**0.048**
Ganyu	217/469	569/1,117	1.03(0.84–1.25)	1.03(0.84–1.25)	145/424	**0.68(0.52–0.88)**	**0.69(0.53–0.89)**	**0.007**
Chuzhou	664/827	265/297	1.17(0.95–1.45)	1.17(0.95–1.44)	39/56	0.77(0.49–1.21)	0.79(0.51–1.21)	0.769
Tongshan	96/456	248/1,142	1.01(0.77–1.33)	1.01(0.77–1.32)	87/695	**0.60(0.43–0.83)**	**0.61(0.45–0.84)**	**0.001**
Sex								
Female	569/1,255	249/741	0.94(0.76–1.16)	0.94(0.77–1.16)	48/256	**0.60(0.41–0.86)**	**0.62(0.43–0.87)**	**0.019**
Male	936/2,454	934/2,335	1.02(0.89–1.16)	1.02(0.89–1.16)	233/978	**0.69(0.57–0.83)**	**0.69(0.57–0.84)**	**0.002**
Ever smoking								
No	657/1,962	403/1,612	0.94(0.79–1.11)	0.94(0.79–1.11)	99/718	**0.60(0.46–0.78)**	**0.61(0.47–0.79)**	**0.001**
Yes	848/1,747	780/1,464	1.02(0.88–1.18)	1.02(0.88–1.18)	182/516	**0.73(0.59–0.91)**	**0.74(0.59–0.92)**	**0.032**
Alcohol drinking								
No	829/2,024	442/1,596	0.94(0.80–1.11)	0.94(0.80–1.11)	101/683	**0.63(0.48–0.81)**	**0.63(0.49–0.82)**	**0.002**
Yes	676/1,685	741/1,480	1.02(0.88–1.19)	1.02(0.88–1.19)	180/551	**0.72(0.57–0.90)**	**0.72(0.58–0.90)**	**0.016**
Non-smokers								
County of residence								
Dafeng	178/881	23/195	0.77(0.48–1.25)	0.79(0.50–1.25)	2/22	0.61(0.13–2.88)	0.80(0.29–2.26)	0.231
Ganyu	66/216	131/396	1.16(0.81–1.64)	1.15(0.82–1.61)	31/152	0.76(0.46–1.26)	0.79(0.49–1.26)	0.486
Chuzhou	339/502	104/174	1.02(0.75–1.38)	1.02(0.76–1.37)	16/28	0.71(0.36–1.38)	0.75(0.41–1.38)	0.569
Tongshan	74/363	145/847	0.87(0.63–1.19)	0.87(0.64–1.19)	50/516	**0.51(0.34–0.76)**	**0.54(0.37–0.79)**	**0.001**
Sex								
Female	243/996	202/951	0.88(0.70–1.12)	0.89(0.71–1.12)	57/481	**0.56(0.38–0.82)**	**0.58(0.40–0.85)**	**0.007**
Male	414/966	201/661	1.00(0.78–1.28)	1.00(0.78–1.28)	42/237	**0.62(0.43–0.89)**	**0.64(0.45–0.90)**	**0.027**
Alcohol drinking								

Stratification variables	Never	<2times/week			≥2times/week			p_{trend}[a]
	Case/ Control	Case/ Control	Adjusted OR (95% CI)[a]	SB-Adjusted OR (95% CI)[a]	Case/ Control	Adjusted OR (95% CI)[a]	SB-Adjusted OR (95% CI)[a]	
No	527/1,419	281/1,201	0.91(0.75–1.11)	0.91(0.75–1.11)	71/545	**0.62(0.46–0.84)**	**0.63(0.47–0.85)**	**0.005**
Yes	130/543	122/411	1.00(0.72–1.39)	1.00(0.72–1.38)	28/173	**0.50(0.30–0.83)**	**0.54(0.34–0.87)**	**0.026**
Non-drinkers								
County of residence								
Dafeng	231/904	32/189	0.82(0.54–1.25)	0.83(0.56–1.25)	3/14	0.91(0.24–3.54)	0.96(0.36–2.52)	0.398
Ganyu	78/244	130/423	0.98(0.71–1.36)	0.98(0.71–1.35)	32/163	0.64(0.39–1.03)	0.67(0.42–1.05)	0.110
Chuzhou	448/536	142/168	1.10(0.84–1.45)	1.10(0.84–1.44)	20/27	0.76(0.40–1.43)	0.80(0.45–1.41)	0.968
Tongshan	72/340	138/816	0.84(0.61–1.17)	0.85(0.62–1.17)	46/479	**0.52(0.35–0.79)**	**0.55(0.37–0.81)**	**0.002**
Sex								
Female	498/1,051	222/660	0.94(0.75–1.17)	0.94(0.75–1.17)	43/234	**0.60(0.41–0.88)**	**0.62(0.43–0.90)**	**0.027**
Male	331/973	220/936	0.98(0.78–1.24)	0.98(0.78–1.23)	58/449	**0.66(0.46–0.94)**	**0.68(0.48–0.95)**	**0.054**
Ever smoking								
No	527/1,419	281/1,201	0.91(0.75–1.11)	0.91(0.75–1.11)	71/545	**0.62(0.46–0.84)**	**0.63(0.47–0.85)**	**0.005**
Yes	302/605	161/395	1.00(0.75–1.32)	1.00(0.76–1.31)	30/138	0.63(0.39–1.02)	0.66(0.42–1.04)	0.160

[a]Adjusted for sex (male = 1, female = 0, except for variable of sex), age (continuous), education level (illiteracy = 1, primary = 2, middle = 3, high or college = 4), income 10 years ago (Yuan/year, continuous), body mass index (continuous), family history of esophagus cancer (yes = 1, no = 0), county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4, except for variable of county of residence), pack-year of smoking (continuous, except for variable of ever smoking and analyses among non-smokers), ethanol consumption (ml/week, continuous, except for variable of alcohol drinking and analyses among non-drinkers), and total energy intake (kcal/month, continuous).

Table 5

The joint effects of smoking, alcohol drinking, and raw garlic consumption on esophageal cancer risk

Variables 1	Variables 2	Case/Control	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	Interaction [a]
Pack-years of smoking	**Raw garlic consumption**				
Never smoker	Any	502/2,330	1.00	1.00	RERI: −0.11(−0.24–0.02)
Never smoker	None	657/1,962	1.55(1.36–1.77)	1.23(1.06–1.43)	AP: −0.07(−0.15–0.01)
<30 years	Any	294/764	1.79(1.51–2.11)	1.57(1.31–1.88)	S: 0.83(0.67–1.02)
<30 years	None	319/750	1.97(1.68–2.32)	1.67(1.38–2.01)	**ROR: 0.88(0.80–0.98)**
≥30 years	Any	668/1,216	2.55(2.23–2.92)	2.02(1.72–2.36)	
≥30 years	None	529/997	2.46(2.14–2.84)	1.92(1.62–2.29)	
Alcohol drinking frequency	**Raw garlic consumption**				
Never	Any	543/2,279	1.00	1.00	**RERI: −0.16(−0.28–−0.03)**
Never	None	829/2,024	1.72(1.52–1.95)	1.29(1.12–1.49)	**AP: −0.11(−0.20–−0.02)**
Occasionally	Any	317/836	1.59(1.36–1.87)	1.52(1.28–1.81)	**S: 0.73(0.57–0.93)**
Occasionally	None	229/636	1.51(1.27–1.81)	1.32(1.08–1.61)	**ROR: 0.86(0.77–0.95)**
Often	Any	604/1,195	2.12(1.85–2.43)	1.77(1.51–2.08)	
Often	None	447/1,049	1.79(1.55–2.07)	1.72(1.44–2.05)	
Pack-years of smoking	**Alcohol drinking frequency**				
Never smoker	Never	879/3,165	1.00	1.00	**RERI: 0.16(0.10–0.22)**
Never smoker	Occasionally	157/607	0.93(0.77–1.13)	1.14(0.92–1.40)	**AP: 0.11(0.06–0.15)**
Never smoker	Often	123/520	0.85(0.69–1.05)	1.22(0.97–1.54)	**S: 1.54(1.13–2.08)**
<30 years	Never	212/494	1.55(1.29–1.85)	1.44(1.18–1.75)	**ROR: 1.11(1.04–1.18)**
<30 years	Occasionally	153/357	1.54(1.26–1.89)	1.92(1.53–2.41)	
<30 years	Often	248/663	1.35(1.14–1.59)	1.65(1.37–2.00)	
≥30 years	Never	281/644	1.57(1.34–1.84)	1.45(1.21–1.74)	
≥30 years	Occasionally	236/508	1.67(1.41–1.99)	1.79(1.47–2.18)	
≥30 years	Often	680/1,061	2.31(2.04–2.61)	2.72(2.33–3.19)	

[a]Adjusted for sex (male = 1, female = 0), age (continuous), education level (illiteracy = 1, primary = 2, middle = 3, high or college = 4), income 10 years ago (Yuan/year, continuous), body mass index (continuous), family history of esophagus cancer (yes = 1, no = 0), county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4), pack-year of smoking (continuous, except for variables of smoking), ethanol consumption in 1990s (ml/week, continuous, except for variables of alcohol drinking), and total energy intake (kcal/month, continuous).

Table 6

Joint effect of garlic intake, tobacco smoking, and alcohol consumption on esophageal cancer

Raw garlic consumption	Ever smoking	Alcohol drinking	Case/Control	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
For non-smokers and non-drinkers					
None or <2 times/week	−	−	808/2,620	1.00	1.00
≥2 times/week	−	−	71/545	0.42(0.33–0.55)	0.58(0.44–0.76)
For only smokers					
None or <2 times/week	+	−	463/1,000	1.50(1.31–1.72)	1.41(1.21–1.65)
≥2 times/week	+	−	30/138	0.71(0.47–1.05)	0.84(0.55–1.28)
For only drinkers					
None or <2 times/week	−	+	252/954	0.86(0.73–1.01)	1.15(0.96–1.37)
≥2times/week	−	+	28/173	0.53(0.35–0.79)	0.74(0.49–1.14)
For both smokers and drinkers					
None or <2 times/week	+	+	1,165/2,211	1.71(1.54–1.90)	2.03(1.77–2.33)
≥2 times/week	+	+	152/378	1.30(1.06–1.60)	1.71(1.36–2.15)

[a]Adjusted for sex (male = 1, female = 0), age (continuous), education level (illiteracy = 1, primary = 2, middle = 3, high or college = 4), income 10 years ago (Yuan/year, continuous), body mass index (continuous), family history of esophagus cancer (yes = 1, no = 0), county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4), and total energy intake (kcal/month, continuous).