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ESOPHAGEAL CANCER

Association of smoking, alcohol drinking and dietary factors with esophageal cancer in high- and low-risk areas of Jiangsu Province, China

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Abstract

AIM: To study the main environmental and lifestyle factors that account for the regional differences in esophageal cancer (EC) risk in low- and high-risk areas of Jiangsu Province, China.

METHODS: Since 2003, a population-based case-control study has been conducted simultaneously in low-risk (Ganyu County) and high-risk (Dafeng County) areas of Jiangsu Province, China. Using identical protocols and pre-tested standardized questionnaire, following written informed consent, eligible subjects were inquired about their detail information on potential determinants of EC, including demographic information, socio-economic status, living conditions, disease history, family cancer history, smoking, alcohol drinking, dietary habits, frequency, amount of food intake, etc. Conditional logistic regression with maximum likelihood estimation was used to obtain Odds ratio (OR) and 95 % confidence interval (95% CI), after adjustment for potential confounders.

RESULTS: In the preliminary analysis of the ongoing study, we recruited 291 pairs of cases and controls in Dafeng and 240 pairs of cases and controls in Ganyu, respectively. In both low-risk and high-risk areas, EC was inversely associated with socio-economic status, such as level of education, past economic status and body mass index. However, this disease was more frequent among those who had a family history of cancer or encountered misfortune in the past 10 years. EC was also more frequent among smokers, alcohol drinkers and fast eaters. Furthermore, there was a geographic variation of the associations between smoking, alcohol drinking and EC risk despite the similar prevalence of these risk factors in both low-risk and high-risk areas. The dose-response relationship of smoking and smoking related variables, such as age of the first smoking, duration and amount were apparent only in high-risk areas. On the contrary, a dose-response relationship on the effect of alcohol drinking on EC was observed only in low-risk areas.

CONCLUSION: The environmental risk factors, together with genetic factors and gene-environmental interactions might be the main reason for this high-risk gradient in Jiangsu Province, China.

Key words: Esophageal cacner; Case-control study; Smoking; Alcohol drinking; Dietary factors

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INTRODUCTION

Esophageal cancer (EC) is the sixth most common cause of cancer mortality worldwide. The incidence of this disease shows a striking geographic variation in the world; a 20-fold variation is observed between high-risk China and low-risk western Africa[1]. Jiangsu Province, southeastern China is one of the highest EC incidence areas with a mortality rate of 30.0/100 000 between 1990-1992, which was significantly higher than the national average of 17.0/100 000[2,3]. EC has been the third leading cause of cancer mortality in Jiangsu Province since the 1970s[3]. Although the mortality rates of EC are high in most counties of Jiangsu, national surveys conducted in the 1970s and 1990s have shown that rates differ considerably between different counties within the province, despite their similar geographic characteristics and socioeconomic status[3,4].

Comprehensive studies on the etiology and carcinogenesis of EC in high-risk areas have been carried out during the past decades. Epidemiological evidence suggests that the independent risk factors, tobacco smoking and alcohol drinking, are strongly associated with EC risk and have approximately multiplicative joint effects[5-7]. Dietary factors were also found to play an important role in the development of EC. Increased risk of EC was found to be associated with low intake of raw vegetables and fresh fruits, a deficiency in vitamins or protective antioxidants (e.g. Vitamin C and E, β-carotene, and selenium), high intake of carcinogens (frequent consumption of pickled vegetables and fungi toxins) and thermal injuries (fast eating speed for hot drinks and soups)[8-10]. While the contributory factors of EC are the high consumption of tobacco and alcoholic beverages in Western countries, the causative factors of EC in high-risk areas of China are nutrition deficiency, N-nitrosamines, fungi toxins and genetic factors[11].

Although numerous epidemiological studies have been conducted to explore the associations between environmental, lifestyle, dietary factors and the risk of esophageal cancer, few studies have been conducted to compare the association between risk factors and EC in apparently similar areas with a high risk gradient. Thus, a population-based case-control study has been conducted since 2003 in both low and high-risk areas of Jiangsu Province, China to study main environmental and lifestyle factors that account for regional differences in EC risk.

This paper reports the preliminary results on the independent and joint effects of smoking, alcohol drinking and dietary factors on EC risk and compares their associations with EC in both high-risk and low-risk areas.

MATERIALS AND METHODS

Study area

This study has been conducted in Dafeng and Ganyu counties since late 2003. Both counties are less developed coastal areas in northern Jiangsu Province, China, with 0.7 million and 1.1 million inhabitants, respectively. Dafeng is a high cancer incidence area and has a much higher mortality rate of EC than Ganyu. From 1996 to 2002, the yearly average age-adjusted mortality rate of EC in Dafeng was 36/100 000, whereas Ganyu had a considerably lower age-adjusted EC mortality rate of 24/100 000 during the same period ($P < 0.01$)[12].

Selection of cases and controls

Cases Newly diagnosed patients with primary esophageal cancer were recruited using data from regional cancer registry agencies. The cancer registry agencies in both counties were established in the late 1990s and are connected to the local Center for Disease Control and Prevention (CDC). All cases were coded according to the International Classification of Diseases, tenth revision (ICD-10, code C15.0 to C15.9). Secondary and recurrent cancers were excluded. All cases were restricted to local inhabitants of the two counties who have lived in either area for at least 5 years. In 2004, 45% and 72% of all newly registered EC cases were recruited and interviewed in Dafeng and Ganyu, respectively. The comparatively low response rate in Dafeng was partly due to the low involvement of local hospitals during the beginning of the study. A small number of cases were also unwilling to participate. Presently, the response rate in Dafeng is much higher. A system of rapid case recognition was used in the study. All regional hospitals were required by the local health authorities to report new EC patients shortly after diagnosis. As the cancer registry agencies are connected to the local CDC, the field investigators from the local CDC were able to identify and interview most patients within one month after their diagnosis. Of all the EC cases in Dafeng, 46% were histologically confirmed, 40% and 13% were diagnosed by endoscopy and radiology, respectively. In Ganyu, 30% of EC cases were histologically confirmed, 50% and 16% were diagnosed by endoscopy and radiology, respectively.

Controls Cases and controls were individually matched and derived from the same county. The criteria for the eligibility of controls were established as: controls had to be the same gender and within 5 years of age as the case, had to have lived in the area for at least 5 years, and had to have had good physical and mental health to answer questions reliably. Controls were randomly selected by a computer from the demographic database of the general population in the county police station. Local interviewers were responsible for locating and interviewing controls. If a selected control refused to participate, a replacement was found using the same recruitment criteria. The response rate of controls in both Dafeng and Ganyu was around 70%. Till March 2005, more than 400 EC cases were recruited in each county. However, the control recruitment rate is slower than the rate of case identification; thus only 291 and 240 pairs of cases and their matched controls were used in this analysis.

Data collection

Identical protocols and pre-tested standardized questionnaires were used. Data collection included a written informed consent, a face-to-face interview, a physical examination, and a 5 ml blood sample taken by professional interviewers from the local CDC in both counties. The questionnaire elicited detailed information on potential determinants of EC, including demographic information, socio-economic status, living conditions, disease history, family cancer history (any malignant neoplasm in first-degree relatives), smoking, alcohol drinking, dietary habits, and frequency and amount of food intake.

In our study, never-smokers were defined as having smoked fewer than 100 cigarettes in their lifetime. Current smokers and drinkers were defined as those who had the habit during the time of interview or those who stopped the habit because of health problems within one year of the date of interview. The dietary questionnaire used in this study included 90 food items. For each food item, the amount and frequency of consumption over the past year were inquired. For cases, the amount and frequency of consumption referred to the year prior to the onset of the disease. In the final analysis, foods were categorized into several major groups: staple foods, preserved foods, meat, fish, eggs, soybean, and fruits and vegetables.

An anthropometric measurement and physical examination also took place at the time of interview to evaluate the subject's health status. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (i.e., kg/m^2). BMI was grouped into quartiles according to the Chinese national standard (underweight: <18.5, normal: 18.5-23.9, overweight: 24~27.9, obesity: ≥28)[13].

Statistical analysis

Data were double entered using Epidata 2.1b and cleaned and analyzed using SAS v8.2. Chi-square and Student *t*-tests were used to compare the distribution of relevant factors among the control groups between the two counties. Conditional logistic regression with maximum likelihood estimation of parameters was applied for both univariate and multivariate analyses. This was done by transforming each matched pair into a single observation, where the explanatory variable value was the difference between the corresponding values for the case-control pair [14]. Continuous variables such as income level and amount of food intake were divided into quartiles based on the frequency distribution among control groups.

The strength of the association was quantified as odds ratio (OR) obtained from conditional logistic regression. Statistical significance was set at 0.05, and accordingly, 95% confidence interval (CI) around the OR was used to address precision.

RESULTS

Subject characteristics

There were 291 pairs of cases and controls (200 male and 91 female pairs) in Dafeng and 240 pairs (181 male and 59 female) in Ganyu, respectively. By design, cases and controls had similar distributions in terms of gender and age in both two counties (Table 1). The differences in the distribution of the above-mentioned variables between the two counties were examined by comparing the two control groups. The proportion of patients who were older than 70 years of age and the proportion of illiteracy in Ganyu were higher than that of Dafeng ($P = 0.002$ and $P < 0.001$, respectively). There was also a geographic variation between the two counties between the proportion of BMI ($P = 0.014$), occurrences of misfortunes such as fire disasters, lost of family members, divorces, etc in the past 10 years ($P = 0.008$) and family history of cancer ($P < 0.001$). On the other hand, there was no significant difference in past economic status, ever-smoking and ever-alcohol drinking habits between the two counties.

Socio-economic status

EC occurred less in higher socio-economic groups characterized by high levels of education and high economic status in both counties (Table 2). On the contrary, low levels of education, low economic status, family history of cancer in first-degree relatives (Dafeng OR: 1.53, Ganyu OR: 2.07), and occurrences of misfortune in the past 10 years (Dafeng OR: 1.26, Ganyu OR: 1.64) increased the risk of developing EC in both areas. In Dafeng, when compared to the lowest quartile (underweight people) of BMI, the second quartile (normal weight people, OR = 0.45) and the third quartile (overweight people, OR = 0.26) significantly showed a reduced risk of EC; whereas the OR increased in the highest quartile (obese people, OR = 0.49). A similar association between BMI and EC risk was also found in Ganyu, although the trend was not significant.

Tobacco smoking and alcohol drinking

Consistent smoking elevated the risk of developing EC in both counties (Table 3). In Dafeng, former smokers and current smokers have a 1.93- and 2.42- fold higher risk of developing EC than never-smokers. In Ganyu former smoking and current smoking also increased the risk of developing EC (OR = 1.28 and 2.36 respectively). We found in Dafeng that smoking at an earlier age (for trend $P = 0.016$), long durations of smoking (for trend $P = 0.006$), and large amounts of cigarettes per day (for trend $P = 0.029$) were significantly associated with increased EC risk, with an apparent dose-response relationship. However, these associations were not significant in Ganyu.

In Ganyu, subjects who had drunk alcohol tended to have a higher risk of EC (OR = 1.71, 95% CI: 1.02-2.88). Moreover, drinking at an early age (for trend $P = 0.012$) and long durations of drinking (for trend $P = 0.061$) showed an increasing association with EC (Table 4). A high consumption of pure ethanol per week, 10 years ago, slightly elevated the risk of EC, but no significant dose-response relationship was found. We did not find any significant association between alcohol drinking and EC in Dafeng, despite its similar alcohol drinking prevalence as Ganyu. The joint effects by smoking and alcohol drinking were also explored in both counties, but no significant interaction was observed either in Dafeng ($P = 0.900$) or in Ganyu ($P = 0.870$).

Dietary factors

After adjusting for potential confounders in both Dafeng and Ganyu, subjects with fast eating speeds showed an increased risk of developing EC (Dafeng: OR=4.01; Ganyu: OR=3.09). On the other hand, high food temperatures, the possibility of being exposed to grain fungi pollution, and frequent intake of fresh garlic did not influence EC risk significantly (Table 5).

With regard to the consumption of major food groups, high consumptions of fish and seafood products significantly elevated the risk of developing EC in Dafeng (for trend $P = 0.024$). Staple foods, preserved foods, fruits and vegetables, and soybean, however, were not apparently associated with EC risk in either county.

DISCUSSION

This population-based case-control study, conducted in high and low-risk areas of Jiangsu Province, China demonstrated an association between tobacco smoking, alcohol drinking, dietary factors and EC. These

Table 1 Characteristics among EC cases and controls in Dafeng and Ganyu[1] *n* (%)

Characteristics	Dafeng (high-risk)		Ganyu (low-risk)		*P* value[2]
	Case (*n* = 291)	Control (*n* = 291)	Control (*n* = 240)	Case (*n* = 240)	
Gender: Male	200 (68.7)	200 (68.7)	181 (75.4)	181 (75.4)	
Female	91 (31.3)	91 (31.3)	59 (24.6)	59 (24.6)	0.088
Age (yr) Mean±SD	64.8 ± 8.6	64.6 ± 8.9	65.4 ± 10.3	65.6 ± 10.4	
<50	14 (4.8)	17 (5.8)	19 (7.9)	17 (7.1)	
50-59	61 (30.0)	59 (20.3)	48 (20.0)	51 (21.3)	
60-69	137(47.1)	137 (47.1)	78 (32.5)	76 (31.7)	0.002
70-79	71 (24.4)	69 (23.7)	77 (32.1)	78 (32.5)	
≥80	8 (2.8)	9 (3.1)	18 (7.5)	18 (7.5)	
Level of education					
Illiterate	156 (53.6)	130 (44.7)	138 (57.7)	164 (68.6)	
Primary school	95 (32.7)	119 (40.9)	63 (26.4)	54 (22.6)	<0.001
Secondary school & above	40 (13.7)	42 (14.4)	38 (15.9)	21 (8.8)	
Past economic status					
(By separate cut-off points)					
Median (CNY/yr)	1250	1500	1000	775	
1 (lowest)	97 (33.5)	55 (19.0)	38 (16.2)	47 (20.3)	
2	68 (23.5)	64 (22.1)	71 (30.2)	87 (37.5)	
3	73 (25.2)	96 (33.1)	71 (30.2)	59 (25.4)	0.235
4 (highest)	52 (17.9)	75 (25.9)	55 (23.4)	39 (16.8)	
Smoking status[3]					
Neversmoker	92 (31.6)	122 (41.9)	95 (39.6)	82 (34.2)	
Former-smoker	71 (24.4)	64 (22.0)	19 (7.9)	17 (7.1)	0.067
Current smoker	128 (44.0)	105 (36.1)	126 (52.5)	141 (58.7)	
Alcohol drinking status[4]					
Never drinker	175 (60.1)	181 (62.2)	143 (59.6)	131 (54.6)	
Former drinker	5 (1.7)	7 (2.4)	7 (2.9)	7 (2.9)	0.076
Current drinker	111 (38.1)	103 (35.4)	90 (37.5)	102 (42.5)	
Encountered misfortune in past10 yr:					
No					
Yes	54 (18.6)	41 (14.2)	33 (14.0)	54 (23.3)	
	237 (81.4)	248 (85.8)	203 (86.0)	178 (76.7)	0.008
History of family cancer					
No	112 (38.5)	86 (29.6)	16 (6.7)	29 (12.1)	
Yes	179 (61.5)	205 (70.5)	224 (93.3)	211 (87.9)	<0.001
Body mass index					
<18.5	60 (20.8)	27 (9.3)	18 (7.6)	31 (13.4)	
18.5-23.9	182 (63.0)	192 (66.2)	161 (67.9)	155 (67.1)	0.014
23.9-27.9	34 (11.8)	60 (20.7)	46 (19.4)	28 (12.1)	
≥28	13 (4.5)	11 (3.8)	12 (5.1)	17 (7.4)	

[1] Some strata do not match the total because of missing values; [2] The *P*-value for comparing the distribution of factors between the two counties; [3] Never-smokers and ever-smokers were used for comparing the smoking habits between the two counties; [4] Because of the few numbers of former drinkers in both two counties, alcohol drinking status was categorized to never-drinkers and ever-drinkers for the comparison between the two counties and following analyses.

associations were compared separately in the two regions which had similar socioeconomic status and geographic characteristics. From our awareness, this is the first comparative population-based case-control study conducted in low-risk and high-risk areas simultaneously to compare the different associations of risk factors and EC in similar areas with high-risk gradients. Like other epidemiological researches, our study showed that EC was inversely associated with socioeconomic status, such as level of education and income. However this disease was more frequent among subjects with smoking and alcohol drinking habits and unhealthy dietary factors. Furthermore, a geographic variation of some associations was observed between the low-risk and high-risk areas. Smoking elevated the risk of EC in both areas concordantly, but the dose-response relationship of smoking and smoking related variables (age of first smoking, duration and amount) was apparent only in the high-risk area. On the contrary, the effect of alcohol drinking on EC and a dose-response relationship was only observed in the low-risk area.

Supporting previous studies, the risk of EC was inversely associated with socioeconomic status in the present study[15,16]. People with higher levels of education and better financial situations tend to have a lower risk of developing EC due to good living conditions and better health care access. Increased risk was found in people who had encountered misfortune in the past 10 years (Dafeng OR: 1.26, Ganyu OR: 1.64), or had a history of family cancer in first-degree relatives (Dafeng OR: 1.53, Ganyu OR: 1.57). These results were consistent in both high-risk and low-risk areas.

Associations between body mass index (BMI) and EC have been explored in several studies. Chow *et al*[17] reported a tendency towards a decreasing risk of esophageal squamous cell carcinoma with increasing BMI. Engeland found that low BMI increased the risk

Table 2 OR[1] and 95% CI of socioeconomic status in EC of Dafeng and Ganyu

Socioeconomic status	Dafeng (high-risk)	Ganyu (low-risk)
Level of education		
Illiterate	1.00 (Referent)	1.00 (Referent)
Primary school	0.54 (0.35-0.84)	0.58 (0.33-1.03)
Secondary school & above	0.74 (0.39-1.41)	0.42 (0.21-0.83)
P value for trend	0.08	0.008
Past economic status		
1 (lowest)	1.00 (Referent)	1.00 (Referent)
2	0.67 (0.43-1.06)	1.03 (0.61-1.75)
3	0.44 (0.28-0.68)	0.76 (0.44-1.31)
4 (highest)	0.39 (0.23-0.65)	0.73 (0.41-1.28)
P value for trend	<0.001	0.024
Encountered misfortune in past 10 yr		
No	1.00 (Referent)	1.00 (Referent)
Yes	1.26 (0.80-1.98)	1.64 (0.98-2.73)
History of family cancer		
No	1.00 (Referent)	1.00 (Referent)
Yes	1.53 (1.06-2.19)	2.07 (1.03-4.17)
Body mass index		
<18.5	1.00 (Referent)	1.00 (Referent)
18.5-23.9	0.45 (0.26-0.76)	0.50 (0.28-0.90)
23.9-27.9	0.26 (0.13-0.50)	0.36 (0.17-0.75)
≥28	0.49 (0.18-1.33)	0.80 (0.33-1.98)
P value for trend	0.002	0.376

[1] Matched by age and gender, further adjusted for education level and past economic status (quartile).

Table 3 OR[1] and 95% CI of tobacco smoking in EC of Dafeng and Ganyu

Tobacco smoking	Dafeng (high-risk)	Ganyu (low-risk)
Smoking status[2]		
Former smoker	1.93 (0.91-4.08)	1.28 (0.28-5.83)
Current smoker	2.42 (1.28-4.56)	2.36 (0.89-6.26)
P value for trend	0.005	0.07
Age at first smoke[2]		
<20	2.02 (0.93-4.38)	1.60 (0.31-7.90)
20-34	2.32 (1.15-4.67)	2.25 (0.80-6.35)
≥35	1.80 (0.62-5.24)	0.98 (0.29-3.24)
P value for trend	0.016	0.249
Duration of smoking (yr)[2]		
1-29	1.61 (0.67-3.86)	1.44 (0.46-4.42)
30-49	2.65 (1.28-5.49)	2.04 (0.60-6.92)
≥50	2.04 (0.78-5.35)	1.98 (0.43-9.11)
P value for trend	0.009	0.194
Amount of smoking (Cig/d)[2]		
1-9	1.36 (0.50-3.74)	1.12 (0.27-4.68)
10-19	2.21 (1.01-4.80)	1.56 (0.42-5.78)
≥20	2.04 (1.00-4.18)	0.91 (0.32-2.61)
P value for trend	0.015	0.915
Total consumption of cigarettes[2]		
1 (lowest)	1.40 (0.61-3.21)	0.96 (032-2.82)
2	2.55 (1.06-6.14)	3.50 (0.37-32.8)
3	1.88 (0.79-4.49)	1.94 (0.25-14.7)
4 (highest)	1.81 (0.57-5.74)	0.74 (0.19-2.81)
P value for trend	0.029	0.959

[1] Matched by age and gender, further adjusted for level of education, past economic status (group) and alcohol drinking; [2] Never-smokers were used as the reference group.

Table 4 OR[1] and 95% CI of alcohol drinking in EC of Dafeng and Ganyu

Alcohol drinking	Dafeng (high-risk)	Ganyu (low-risk)
Alcohol drinking		
Never	1.00 (Referent)	1.00 (Referent)
Ever	1.01 (0.70-1.46)	1.71 (1.02-2.88)
P value	0.964	0.043
Age of first drink[2]		
<20	0.83 (0.44-1.58)	2.59 (1.03-6.50)
20-34	1.23 (0.79-1.91)	1.95 (1.08-3.53)
≥35	0.81 (0.48-1.35)	1.18 (0.56-2.47)
P value for trend	0.815	0.012
Duration of drinking (yr)[2]		
1-24	0.96 (0.56-1.59)	1.28 (0.58-2.79)
25-34	0.89 (0.48-1.64)	1.48 (0.75-2.94)
35-44	1.57 (0.92-2.70)	1.47 (0.71-3.01)
≥45	0.77 (0.43-1.40)	1.88 (0.95-3.75)
P value for trend	0.834	0.061
Alcohol consumption 10 years ago[2] (pure ethanol mL/wk)		
1-249	0.87 (0.49-1.54)	0.79 (0.36-1.74)
250-499	1.06 (0.60-1.89)	0.61 (0.30-1.25)
500-749	0.97 (0.52-1.79)	1.63 (0.77-3.43)
≥750	1.10 (0.63-1.93)	1.27 (0.71-2.28)
P value for trend	0.74	0.223

[1] Matched by age and gender, further adjusted for level of education, past economic status (group) and tobacco smoking; [2] Never-drinkers were used as the reference group.

of esophageal squamous cell carcinoma, while high BMI increased the risk of esophageal adenocarcinoma. In general, lowest BMI had the highest risk of EC[18]. Our study found similar results in both low-risk and high-risk areas. The risk of developing EC was significantly lower in normal and overweight groups when compared to the underweight group. However, the OR was high in the obese group. An increased risk of esophageal adenocarcinoma among obese persons has been explained by a dose-dependent association between increasing BMI and the risk of gastro-esophageal reflux symptoms, as observed by Nilsson *et al*[19].

In conformity with other epidemiological studies shown in Western countries and some areas of Asia and Africa[20-22], increased risks of EC among former smoking and current smoking subjects were observed in both areas of our study. Tobacco smoke contains over 3000 constituents including 30 carcinogens, such as polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and N-nitrosamines. The metabolites of these carcinogens may lead to gene mutation and cancer[23]. Age of first smoke, duration and dosage of tobacco use were also strongly associated with an elevated risk of developing EC in Dafeng, with an apparent dose-response relationship. Although Ganyu had a similar smoking prevalence, these time and dosage dependent results were not statistically significant in this area.

Several studies have reported a strong correlation between EC and alcohol abuse[24,25]. Alcoholic beverages also contain carcinogens and other compounds and may facilitate the absorption of esophageal mucosal cells and make them more susceptible to chemical carcinogens[26]. On the contrary of tobacco smoking, the positive association between alcohol drinking and EC was only found in Ganyu in our study (OR=1.71). Several studies

Table 5 OR and 95% CI of dietary habits, food consumption in EC of Dafeng and Ganyu

Dietary factor	County	Category				P value for trend
		1 (lowest)	2	3	4 (highest)	
Food temperature[1]	Dafeng	1	0.51 (0.24-1.09)	-	-	0.08
(1-Normal; 2- Hot)	Ganyu	1	1.14 (0.55-2.41)	-	-	0.714
Eating speed[1]	Dafeng	1	4.01 (1.87-8.62)	-	-	<0.001
(1-Normal; 2-Fast)	Ganyu	1	3.09 (1.24-7.70)	-	-	0.015
Self reported grain fungi pollution[1]	Dafeng	1	2.27 (0.79-6.54)	-	-	0.131
(1-Likely; 2-Not likely)	Ganyu	1	1.18 (0.45-3.11)	-	-	0.741
Fresh garlic/wk[2,3]	Dafeng	1	0.64 (0.26-1.60)	-	-	0.337
	Ganyu	1	1.17 (0.57-2.41)	-	-	0.664
Staple foods[1]	Dafeng	1	0.45 (0.19-1.10)	0.54 (0.21-1.38)	0.73 (0.26-2.04)	0.474
	Ganyu	1	0.98 (0.10-9.77)	0.45 (0.05-4.38)	0.54 (0.05-4.34)	0.324
Meat[4]	Dafeng	1	0.73 (0.29-1.85)	1.66 (0.68-4.10)	1.93 (0.64-5.77)	0.16
	Ganyu	1	0.54 (0.12-2.42)	1.17 (0.28-4.92)	0.65 (0.11-3.67)	0.305
Fish and seafood products[4]	Dafeng	1	1.14 (0.64-2.03)	2.11 (1.12-3.96)	1.91 (1.00-3.64)	0.023
	Ganyu	1	0.98 (0.42-2.28)	0.64 (0.28-1.44)	1.04 (0.46-2.33)	0.794
Eggs[4]	Dafeng	1	0.53 (0.20-1.44)	1.23 (0.54-2.80)	1.99 (0.72-5.49)	0.146
	Ganyu	1	0.69 (0.28-1.73)	0.30 (0.10-1.10)	0.95 (0.41-2.22)	0.936
Soybean[4,5]	Dafeng	1	1.81 (0.88-3.74)	-	-	0.11
	Ganyu	1	1.31 (0.37-4.59)	-	-	0.677
Preserved foods[4]	Dafeng	1	0.26(0.09-0.75)	0.49 (0.16-1.46)	0.94 (0.37-2.36)	0.635
	Ganyu	1	1.05 (0.37-2.97)	0.56 (0.21-1.48)	1.21 (0.46-3.20)	0.932
Vegetables[4]	Dafeng	1	1.26 (0.50-3.16)	0.94 (0.39-2.30)	1.37 (0.49-3.83)	0.72
	Ganyu	1	0.34 (0.08-1.54)	0.80 (0.20-3.18)	0.76 (0.15-3.72)	0.889
Fruits[2]	Dafeng	1	1.02 (0.42-2.47)	0.42 (0.16-1.12)	1.23 (0.51-2. 98)	0.802
	Ganyu	1	1.61 (0.68-3.80)	1.13 (0.43-2.95)	1.17 (0.41-3.37)	0.746

[1] Matched by age and gender, further adjusted for level of education, past economic status (group), smoking, alcohol drinking, BMI group, cancer family history, eating speed, food temperature and self-reported grain fungi pollution; [2] Matched by age and gender, further adjusted for education level, past economic status (group), smoking, alcohol drinking, BMI group, eating speed and family history of cancer; [3] Less than 3 times per week=1, 3 times per week and above=2; [4] Matched by age and gender, further adjusted for level of education, past economic status (group), smoking, alcohol drinking, BMI group, cancer family history, eating speed and food temperature; [5] Categorized by median among controls.

have reported a linear relationship between an overall daily ethanol consumption and EC risk[27,28]. However, in our study only the age of initial drinking and years of alcohol drinking were found to be associated with EC risk in Ganyu. No clear relationship between daily alcohol consumption and EC was found.

The interaction between tobacco smoking and alcohol drinking has been studied in many researches. It has been suggested that alcohol and tobacco interact in a multiplicative way[29,30]. In a large scale study, Castellsagué reported that the risk of EC in the highest joint level of alcohol and cigarette smoking increased 50.85-fold and 35.34-fold among men and women[7]. However the joint effect of smoking and alcohol was not found to be statistically significant in the high-risk area and the low-risk area in our study. The link between smoking, alcohol and EC in China are not as apparent as in Western countries. Several previous studies conducted in other high-risk areas of Jiangsu, China either did not find any relation or found only a weak association between smoking, alcohol drinking and EC[31,32].

Dietary factors are thought to play an important role in the pathogenesis of EC. Some epidemiological studies have suggested that the risk of EC is inversely associated with a higher intake of fruits and vegetables[33,34], while a detrimental effect was observed among high intake of certain types of meat, butter and saturated fatty acids[35]. Increased risk was related to N-nitrosamine compounds (mainly from preserved foods), foods contamination by fungus and the presence of toxins. Some unhealthy dietary habits such as fast eating speeds, consumption of hot foods and soups can cause the injury of esophageal mucosa and render the mucosa more susceptible to carcinogens.

An increased OR was found among fast eating subjects in both areas of this study (Dafeng OR: 4.01, Ganyu OR: 3.09). However, the associations between high food temperatures, the possibility of fungi pollution of grain, frequent intake of fresh garlic and EC was not statistically significant. In the food group analysis, after adjusting for potential confounders, we did not find any significant association between major food consumption and EC risk in either area. A positive association of fish and seafood product intake in Dafeng was found (for trend $P = 0.024$). Fish is a rich dietary source of n-3 fatty acids. It has been reported that this long chain of fatty acid can suppress mutation, inhibit cell growth, and enhance cell apoptosis, thus reducing the risk of developing cancer[36]. The contradicting results found in our study of the increased risk found in the association between fish consumption and EC in Dafeng was probably due to water contamination or other unidentified confounders. However, this hypothesis needs to be further clarified and studied. Moreover, it may be more reasonable to study food composition and micronutrients in our future analysis rather than to use individual foods or food groups[37].

Ganyu has a high proportion of ageing and illiterate residents. The economic status of residents in Ganyu is also lower than Dafeng, although the difference is not significant (Table 1). As disease is more prevalent among ageing populations and the level of education and economic situation are inversely associated with the risk of developing EC, it can be expected that the two counties would have a far higher risk gradient if they had a similar distribution of age and socioeconomic related factors.

As mentioned above, a heterogeneous association between smoking, alcohol drinking and EC was observed in the low- and high-risk areas in our study, despite their similar geographic characteristics and general socioeconomic statuses. A malignant tumor is the result of a series of DNA alterations in a single cell, which leads to a loss of normal functioning. A large number of gene coding for enzymes and receptors are involved in xenobiotic metabolism, with many of them showing polymorphisms. Many molecular epidemiological studies have proved that polymorphisms in activation and detoxification enzymes can interact with environmental carcinogens. It has been reported that GSTM1 null carriers may be especially susceptible to the action of tobacco with regards to EC[38], while inactive the ALDH2 genotype increases the risk of EC in alcoholics[39]. Genetic polymorphisms can interact with dietary factors. For example, cruciferous vegetables can inhibit the metabolic activation of phase I enzymes and induce the detoxification of carcinogens via phase II enzymes[40]. The polymorphism of one gene may also have an effect on other genes. Gene-gene interactions between GSTM1 0/0 and CYP1A1 and CYP1A2 enzyme induction have been observed in smokers[41]. Another example is that individuals with CYP1A1 Ile/Val alleles have greater CYP1A2 activity than those with wild type CYP1A1[42]. Furthermore, it has been suggested that genes can influence individual behaviours such as smoking, alcohol drinking and excess calorie intake, thereby having the potential to affect cancer risk[43].

Both environmental factors and human genes can show considerable regional variability. The variation in these factors together with their separate and joint effects ultimately determine the risk of cancer in different regions and may be the main reason for the large EC risk gradient between the counties in Jiangsu Province. Unfortunately scientific evidence on genetic polymorphisms, gene-environmental and gene-gene interactions remains inconsistent and inconclusive because of low statistical power and few candidate genes in previous studies. Moreover, no study has ever been conducted to compare the association between gene-environmental interaction and EC risk in apparently similar areas with a high risk gradient. Therefore, our future study will focus on genetic polymorphisms and their interactions with different environmental, lifestyle and dietary factors in the etiology of EC in high and low-risk areas, with a sufficient sample size and candidate genes.

Our present population-based case-control study has some limitations. Differences in the etiological factors between esophageal adenocarcinoma and squamous cell carcinoma may exist. Because of the low histological examination rate in China, it is difficult to differentiate between the subtypes of EC in a population-based study. Additionally, most risk factors in our study are based on self-reported data and may be subject to recall bias. Moreover, the relationship between BMI and EC was examined by using height and weight measurements obtained at the time of interview. Some cases might have begun to lose weight at an earlier time because of the disease. This factor could also have caused bias in our study.

In summary, the present study demonstrated the association between smoking, alcohol drinking, dietary factors and EC risk in the low-risk and high-risk areas of Jiangsu Province, China. Heterogeneous effects of smoking and alcohol drinking were found between the two areas, despite their similar geographic characteristics and general socioeconomic status. The variation in environmental risk factors, together with gene-environment and gene-gene interactions may be the main reason for these heterogeneous associations and may contribute to the large risk gradient of EC mortality in Jiangsu Province, China.

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