Effect of the interaction between the amount and duration of alcohol consumption and tobacco smoking on the risk of esophageal cancer: A case-control study

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Abstract. The effects of alcohol consumption and tobacco smoking on the prevalence of esophageal cancer vary considerably by country, race and lifestyle. Few data exist on the effect of the interaction between the amount and duration of alcohol consumption and tobacco smoking on the incidence of esophageal cancer. In this case-control study, the cases included patients with histologically confirmed esophageal squamous cell carcinoma (ESCC) younger than 60 years of age and recruited between January 1, 2002 and December 31, 2006. The controls had no abnormality during a medical checkup. A total of 835 pairs were created by pairing each case to a gender- and age-matched control. Conditional logistic regression analysis was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals. Univariate conditional logistic regression analyses revealed that the ORs according to both duration of alcohol consumption and tobacco smoking increased monotonically. Alcohol consumption and tobacco smoking may have a synergistic effect on the incidence of ESCC. Conditional logistic regression analysis using a forward stepwise selection procedure revealed that the incidence of ESCC was associated with the duration of tobacco smoking, the interaction between the amount and duration of alcohol consumption, and a family history of cancer. In particular, groups with a long duration of alcohol consumption and high alcohol intake had much higher ORs than those with short duration and low intake, which highlights the importance of the interaction between the amount and duration of alcohol intake. This study confirmed the significance of the interaction between alcohol consumption and tobacco smoking in esophageal cancer. This interaction between amount and duration is an accurate indicator for estimating the risk of esophageal cancer attributable to alcohol consumption and tobacco smoking. These findings suggest that decreasing the number of young and middle-aged drinkers and smokers will reduce the incidence of esophageal cancer.

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Introduction

Alcohol consumption and tobacco smoking are established risk factors for esophageal cancer (1-4), and most studies have noted that the dose-response relationship is steep and monotonic. Enzinger and Mayer reported that, in most developed countries, tobacco smoking is associated with a 2- to 4-fold increased risk of esophageal cancer, as compared to non-smokers (5). In addition, Zambon *et al* reported that the esophageal cancer risk rose steeply with increasing alcohol consumption (6). Furthermore, alcohol and tobacco have been reported to interact multiplicatively in the development of esophageal cancer. Brown *et al* indicated that the odds ratio (OR) of esophageal squamous cell carcinoma (ESCC), with regard to heavy exposure to both these factors was 35.4 in white males and 149.2 in black males, as compared to non-smokers/light smokers and drinkers of corresponding race (7).

In general, the risk of cancer incidence is estimated in epidemiological studies by using ORs. However, since incidence is affected by the type of alcohol and tobacco consumed, and by race, diet, genetic diversity in susceptibility to alcohol and tobacco, and other socioeconomic factors, there are considerable differences in the ORs of esophageal cancer for the different countries and regions where such research has been conducted (8-14). Consequently, great care must be taken in the interpretation of these estimated ORs. In addition, ORs must be calculated for each country and region (14).

There have been numerous investigations of the associations of the incidence of esophageal cancer with the amount and duration of alcohol consumption and tobacco smoking,

and with the interaction between and dose-dependency of alcohol consumption and tobacco smoking (7,10,12,15). However, few studies have examined the effects of the interaction between the amount and duration of alcohol consumption and tobacco smoking. Such an examination is of great importance, since the effect on the incidence of esophageal cancer of consuming 40 g of ethanol per day for 10 years may be quite different from that of consuming 20 g of ethanol per day for 20 years, even though the total quantity of ethanol consumed is equal.

This study investigated the independent and combined effects of alcohol consumption and tobacco smoking on the risk of esophageal cancer in Hebei Province, China. In particular, we examined the interaction between the amount and duration of alcohol consumption and tobacco smoking.

Patients and methods

Study design. A matched-pair case-control study was conducted to estimate the individual and combined risks of alcohol consumption and tobacco smoking. The subjects included 835 pairs, each of which consisted of a patient with esophageal cancer (case) and a healthy individual (control) matched by age (±2 years) and gender. Eligible subjects had been residents of the city of Shijiazhuang, Hebei Province, China, for at least 20 years and were younger than 60 years of age. Before being interviewed, the subjects were informed of all study objectives and the content of the research. The research protocol was approved by the Local Ethics Committee and the Research Committee of Hebei Medical University.

Subjects. The cases were drawn from 1,911 patients who had received a diagnosis of primary invasive cancer of the esophagus between January 2002 and December 2006 at the Fourth Hospital of Hebei Medical University in Shijiazhuang. All diagnoses were histologically confirmed and based on the International Classification of Diseases, 10th revision (ICD-10, code C15). From these 1,911 patients, we excluded 235 who had suffered a recurrence of esophageal cancer or had another concomitant cancer, as well as 720 patients who were older than 60 years. Thus, 956 cases remained for inclusion. The pathological diagnosis was squamous cell carcinoma in 835 cases (87.3%), adenocarcinoma in 35 cases (3.7%) and other cancer types in 86 cases (9%). The 835 cases with squamous cell carcinoma – the dominant histological type – were enrolled for case-control matching and subsequent statistical analysis.

Using a physical examination database, 3,076 individuals who lived in the same area (Hebei Province, China) from 2004 to 2006 were enrolled as controls and underwent medical checkups.

Risk factors. The factors and categories used in the study are shown in Table I. Data for the study were obtained from the subjects' medical records and, in the case of controls, from checkups. The information collected included age at diagnosis (for all cases), age at medical checkup (for all controls), gender, alcohol and tobacco use, medical history and family history of cancer. Participants were interviewed to collect details on average daily tobacco use, ages when tobacco smoking began and ended, and duration of smoking.

Information on alcohol consumption consisted of the average grams of ethanol consumed per day, type of alcoholic beverage consumed, lifetime duration of the habit, ages when alcohol consumption began and ended, and number of years since quitting. The type of beverage consumed was classified as baijiu, beer and other liquors. Baijiu is a Chinese distilled alcoholic beverage usually made from sorghum or glutinous rice. It is the most popular drink in China and contains 40-60% ethanol per volume on average. Chinese usually drink baijiu in a single swallow from a 20- to 30-ml glass, without a chaser. The average daily amount of alcohol was calculated using ethanol exchange rates of 40% for baijiu, 5% for beer, 12% for wine and 40% for hard liquor. A non-drinker was defined as someone who consumed less than one drink per month. One drink was defined as 50 ml of baijiu, 400 ml of beer or 50 ml of hard liquor. The total amount of ethanol consumed per day was calculated using the above-mentioned ethanol percentages. The resulting values were converted to grams by multiplying 1 ml of pure ethanol by 0.789 (16).

Finally, the risk factors used in this study were summarized with respect to the amount of alcohol consumed per day, duration of alcohol consumption (years), interaction between the amount and duration of alcohol consumption (the total amount of alcohol consumed over a certain time period), number of cigarettes smoked per day, duration of tobacco smoking (years), interaction between the amount and duration of tobacco smoking (the total amount of tobacco smoked over a certain time period) and family history of cancer. The interaction between the amount and duration of alcohol consumption for 20 g of alcohol per day for 10 years and that for 10 g of alcohol per day for 20 years were distinguished by slightly modifying partial dummy variables, as described in the next section.

Statistical analysis. We performed conditional logistic regression analysis to estimate ORs and corresponding 95% confidence intervals (CIs). A forward stepwise regression method was used to select the best subset of risk factors associated with the incidence of esophageal cancer, after adjusting for the effect of other factors. The candidate factors were the amount of alcohol consumed, duration of alcohol consumption, interaction between the amount and duration of alcohol consumption, amount of tobacco smoked, duration of tobacco smoking, interaction between the amount and duration of tobacco smoking, and family history of cancer. The amount and duration were divided into four categories. These categories were then converted into three categories by using partial dummy variables; the reference category included those individuals who were non-smokers and/or non-drinkers. For the interaction between the amount and duration of tobacco smoking and the interaction between the amount and duration of alcohol consumption, dummy variables were created so that individuals smoking 10 cigarettes per day for 20 years could be discriminated from those smoking 20 cigarettes per day for 10 years, even though the product for both is 200. All statistical analyses were performed using SAS 9.1. A p-value <0.05 was considered statistically significant for all tests.

Table I. Characteristics of the cases and controls.

Factors/categories	No. of subjects (%)		
	Cases	Controls	Total
Age (years)[a]			
<45	78 (9.3)	78 (9.3)	156 (9.3)
45 to <60	757 (90.7)	757 (90.7)	1,514 (90.7)
Gender			
Male	571 (68.4)	571 (68.4)	1,142 (68.4)
Female	264 (31.6)	264 (31.6)	528 (31.6)
Family history of cancer			
Yes	230 (27.5)	122 (14.6)	352 (21.1)
No	605 (72.5)	713 (85.4)	1,318 (78.9)
Duration of alcohol consumption (years)			
0	530 (63.5)	613 (73.4)	1,143 (68.4)
<15	62 (7.4)	59 (7.1)	121 (7.2)
15 to <20	133 (15.9)	122 (14.6)	255 (15.3)
≥20	110 (13.2)	41 (4.9)	151 (9.0)
Amount of alcohol intake (g/day)			
0	530 (63.5)	613 (73.4)	1,143 (68.4)
<30	78 (9.3)	40 (4.8)	118 (7.0)
30 to <60	99 (11.9)	107 (12.8)	206 (12.3)
≥60	128 (15.3)	75 (9.0)	203 (12.2)
Duration of tobacco smoking (years)			
0	427 (51.1)	483 (57.8)	910 (54.5)
<20	56 (6.7)	82 (9.8)	138 (8.3)
20 to <30	160 (19.2)	140 (16.8)	300 (18.0)
≥30	192 (23.0)	130 (15.6)	322 (19.3)
Amount of tobacco smoking (cigarettes/day)			
0	427 (51.1)	483 (57.8)	910 (54.5)
<10	102 (12.2)	69 (8.3)	171 (10.2)
10 to <20	205 (24.6)	203 (24.3)	408 (24.4)
≥20	101 (12.1)	80 (9.6)	181 (10.8)

[a]Age refers to age at diagnosis for cases and age at time of medical checkup for controls.

Results

Subject characteristics. Table I shows the distribution of cases and controls with respect to age, gender and risk factors. There were 757 pairs comprised of participants over the age of 45 years. The proportion of males was 68.4%. Table II shows the distribution of cases and controls for each risk factor. The distribution of exposure to alcohol consumption, tobacco smoking and family history of cancer was asymmetric between cases and controls, i.e., the levels of alcohol consumption and tobacco smoking were higher among cases than among controls. For example, as shown in Table IIB, there were 49 pairs in which the cases consumed 0 to <30 g of ethanol and the controls consumed 0 units; however, there were only 8 pairs in which the cases consumed 0 units and the controls consumed 0 to <30 units. Similarly, the duration of alcohol consumption and tobacco smoking was longer for the cases than for the controls.

Estimation of the risk of alcohol consumption and tobacco smoking by univariate analysis. Conditional logistic regression analysis was performed to estimate the risk of the incidence of esophageal cancer. Table III shows the ORs and corresponding 95% CIs obtained from the univariate conditional logistic regression analysis. With respect to the reference category, the ORs of esophageal cancer increased monotonically with the duration of alcohol consumption and tobacco smoking. Regarding the duration of alcohol consumption, the ORs of esophageal cancer for the categories of 0-15, 15-20 and >20 years were 1.22, 1.26 and 3.10, respectively. The OR of esophageal cancer for alcohol consumption >20 years differed significantly from that for the reference (no consumption of alcohol) category ($p<0.001$). Regarding tobacco smoking, the ORs of esophageal cancer for the categories of 0-20, 20-30 and >30 years were 0.77, 1.29 and 1.67, respectively; the OR for a duration of smoking >30 years was significantly higher than that for non-smokers ($p<0.001$). However, the associations

Table II. Amount and duration of alcohol and tobacco consumption in the matched case-control pairs.

A, Duration of alcohol consumption (years).

Controls	Cases				
	0	<15	15 to <20	≥20	Total
0	515	32	44	22	613
<15	9	10	25	15	59
15 to <20	6	14	48	54	122
≥20	0	6	16	19	41
Total	530	62	133	110	835

B, Amount of alcohol consumption (g/day).

Controls	Cases				
	0	<30	30 to <60	≥60	Total
0	515	49	35	14	613
<30	8	11	17	4	40
30 to <60	5	17	43	42	107
≥60	2	1	4	68	75
Total	530	78	99	128	835

C, Duration of tobacco smoking (years).

Controls	Cases				
	0	<20	20 to <30	≥30	Total
0	384	21	41	37	483
<20	13	11	29	29	82
20 to <30	6	18	58	58	140
≥30	24	6	2	68	130
Total	427	56	160	192	835

D, Amount of tobacco smoking (cigarettes/day).

Controls	Cases				
	0	<10	10 to <20	≥20	Total
0	384	41	36	22	483
<10	6	16	40	7	69
10 to <20	26	35	95	47	203
≥20	11	10	34	25	80
Total	427	102	205	101	835

E, Family history of cancer.

Controls	Cases		
	No	Yes	Total
No	519	194	713
Yes	86	36	122
Total	605	230	835

of the OR for esophageal cancer with the amount of alcohol consumed and with the amount of tobacco smoked were not monotonic.

Interaction between alcohol consumption and tobacco smoking. Table IV illustrates the results of conditional logistic regression analysis of the interaction between alcohol consumption and tobacco smoking. Table IV-A shows the distribution of alcohol consumption and tobacco smoking in the matched pairs. Table IV-B shows the regression coefficients and standard errors of the four possible states, i.e., neither drinking nor smoking, drinking only, smoking only, and both drinking and smoking. Table IV-C shows the estimated ORs of esophageal cancer according to alcohol consumption, tobacco smoking and interaction between the two factors, which were 19.5, 6.2 and 43.8, respectively.

Effect of the interaction between the amount and duration of alcohol consumption and tobacco smoking. Table V shows the ORs for esophageal cancer according to different combinations of alcohol and tobacco amounts and duration. Multiple conditional logistic regression analysis was performed in a forward stepwise manner, and the following seven factors were used as candidates: the amount and duration of tobacco smoking, amount and duration of alcohol consumption, interaction between the amount and duration of tobacco smoking, interaction between the amount and duration of alcohol consumption, and family history of cancer.

Dduration of tobacco smoking, interaction between the amount and duration of alcohol consumption, and family history of cancer were selected as the independent and significant variables. However, the interaction between the amount and duration of tobacco smoking and the amount and duration of alcohol were not selected in this stepwise regression analysis. We found that the OR of the group with the shortest duration and lowest amount of alcohol consumption was 6.99, and that the lowest OR for esophageal cancer among drinkers was 5.23. Individuals who consumed ≥60 g alcohol per day had an OR >40, regardless of the duration of alcohol consumption. Indeed, those consuming ≥60 g alcohol per day for longer than 20 years had an estimated OR of 183.1.

Discussion

Epidemiological studies have shown that the combination of moderate/heavy consumption of alcohol, tobacco smoking, infrequent consumption of raw fruits and vegetables, and low annual income accounts for almost all cases of esophageal cancer (17-21). Among these factors, alcohol consumption and tobacco smoking are the predominant risk factors for this cancer, i.e., the disease is more frequent among smokers and alcohol drinkers. Brown *et al* (24) reported that the population-attributable risk of esophageal cancer due to the combination of alcohol consumption and tobacco smoking was higher than 90% in both whites and blacks in the US (10,19). Studies in other countries have reported similar findings (12,22). However, the ORs for the effects of alcohol and smoking on the incidence of esophageal cancer have varied considerably in well-designed epidemiological studies. Therefore, it would appear desirable to calculate estimates of the risk of esopha-

Table III. Odds ratios (ORs) and 95% confidence intervals (CIs) for each risk factor upon univariate analysis.

Factors	OR	95% CI	P-value
Duration of alcohol consumption (years)			
0	1.00		
<15	1.22	0.84-1.77	0.310
15 to <20	1.26	0.96-1.66	0.090
≥20	3.10	2.13-4.52	<0.001
Amount of alcohol consumption (g/day)			
0	1.00		
<30	2.26	1.51-3.35	<0.001
30 to <60	1.07	0.80-1.44	0.650
≥60	1.97	1.45-2.69	<0.001
Duration of tobacco smoking (years)			
0	1.00		
<20	0.77	0.54-1.11	0.160
20 to <30	1.29	1.00-1.68	0.050
≥30	1.67	1.29-2.16	<0.001
Amount of tobacco smoking (cigarettes/day)			
0	1.00		
<10	1.67	1.20-2.33	0.002
10 to <20	1.14	0.90-1.44	0.260
≥20	1.42	1.04-1.97	0.030

Table IV. Conditional logistic regression analysis of the interaction between alcohol consumption and tobacco smoking.

A, Distribution of alcohol consumption and tobacco smoking in matched pairs of cases and controls.

Controls	Cases				
	Neither	Alcohol consumption only	Tobacco smoking only	Both	Total
Neither	365	11	50	3	429
Alcohol consumption only	3	5	3	43	54
Tobacco smoking only	2	19	98	65	184
Both	3	19	6	140	168
Total	373	54	157	251	835

B, Results of conditional logistic regression analysis.

Variables	Regression coefficient	Standard error
Neither	1.00	-
Alcohol consumption only	2.97	0.48
Tobacco smoking only	1.83	0.38
Both	-1.01	0.45

C, Estimated ORs.

Alcohol consumption	Tobacco smoking	
	No	Yes
No	1.0	6.2
Yes	19.5	43.8

Table V. The odds ratios (ORs) for esophageal cancer, by duration and dose intensity of exposure, as determined by conditional logistic regression analysis.

Factors	Cases	Controls	OR	95% CI	P-value
Duration of tobacco smoking (years)					
0	427	483	-	-	-
<20	56	82	1.71	0.98-2.95	0.060
20 to <30	160	140	3.68	2.23-6.08	<0.001
≥30	192	130	4.76	2.86-7.94	<0.001
Dose intensity of alcohol consumption					
0	530	613	-	-	-
<15 years and <30 g	33	20	6.99	3.14-15.56	<0.001
15 to <20 years and <30 g	27	16	8.86	3.53-22.26	0.002
≥20 years and <30 g	18	4	21.56	5.28-88.06	<0.001
<15 years and 30 to <60 g	19	27	5.23	2.19-12.46	<0.001
15 to <20 years and 30 to <60 g	43	56	9.34	4.13-21.11	<0.001
≥20 years and 30 to <60 g	37	24	13.59	5.34-34.63	<0.001
<15 years and ≥60 g	10	12	45.26	10.53-194.56	<0.001
15 to <20 years and ≥60 g	63	50	49.94	16.65-149.83	<0.001
≥20 years and ≥60 g	55	13	183.12	49.10-682.91	<0.001
Family history of cancer			2.57	1.92-3.43	<0.001
Yes	230	122			
No	605	713			

geal cancer for each country, region and race. The present study quantitatively estimated the effects of alcohol consumption and tobacco smoking on the development of esophageal cancer in Chinese adults who were under the age of 60 years and living in the urban area of Hebei Province. Accompanying the increase in age, physiological function and immunosurveillance of the body appear to decrease in the elderly. There are many factors associated with the differentiation and development of cancer in the body of elderly individuals. In this study, we aimed to clarify the contribution of smoking and alcohol consumption to the development of esophageal cancer. To avoid the interference of numerous factors, we selected individuals below 60 years of age as subjects, as suggested by the World Health Organization, who define an elderly population as one over 60 years of age. Based on this, we focused on the interactive effect of alcohol consumption and tobacco smoking, and the interaction between the amount and duration of drinking and smoking.

The interaction between alcohol consumption and tobacco smoking has been extensively studied, and the results indicate that alcohol and tobacco interact in a multiplicative way (7,19,23). In one large-scale study, Castellsagué *et al* reported that the risk of esophageal cancer among subjects with the highest level of alcohol consumption and highest level of cigarette smoking was increased by 51- and 35-fold in men and women, respectively (11). The present case-control study found that the OR of the interaction between alcohol consumption and tobacco smoking was 43.8, and that alcohol and tobacco interacted in a multiplicative manner, as shown in Table IV. Furthermore, Brown *et al* estimated the joint ORs for alcohol consumption and tobacco smoking stratified by annual income, using a reference group comprising light smokers and light drinkers (24); the ORs of the interaction ranged from 2.0 to 420.6. Thus, our estimated ORs of the interaction between alcohol and tobacco are in accord with those reported in other reliable studies.

Using conditional logistic regression analysis with a forward stepwise method, we identified the interaction between the amount and duration of alcohol consumption, duration of tobacco smoking and family history of cancer as the subset of significant risk factors that contribute to the incidence of esophageal cancer. Our most salient finding is that the interaction between the amount and duration of alcohol consumption (i.e., the average daily alcohol intake multiplied by the duration of intake) is included in this subset of significant and independent risk factors. This suggests that the interaction between the amount and duration of alcohol consumption has more predictive power than when these two factors are considered separately. By contrast, the interaction between the amount and duration of tobacco smoking had weaker predictive power for the incidence of esophageal cancer than the duration of tobacco smoking. As shown in Table V, heavy drinkers had the highest risk for esophageal cancer, particularly those who had been drinking for many years. Almost all alcohol drinkers in China consume baijiu without mixing it with water. Chronic consumption of beverages with a high ethanol content has been implicated in the development and progression of esophageal cancer.

The strength of our study was the use of a case-control design and the enrollment of sufficient numbers of cases and controls in matched pairs to estimate the effects of the interaction between the amount and duration of alcohol consumption and tobacco smoking and the interaction between alcohol and tobacco. However, this population-based case-control study did have some limitations. We estimated the risks for esophageal cancer using information on only alcohol, smoking and

family history of cancer, and did not collect data on other possible risk factors, for example, social status and diet. We were unable to obtain precise data on income and diet in healthy individuals in Hebei Province, particularly among agricultural workers. In addition to alcohol and tobacco, dietary factors may play a causal role in the carcinogenesis of esophageal cancer. Unfortunately, the lack of dietary information made it impossible to evaluate such factors. Finally, due to the very small number of individuals who successfully relinquish alcohol drinking or tobacco smoking, we could not include cessation of alcohol drinking or tobacco smoking as a factor in esophageal cancer.

In conclusion, lifestyle modifications, particularly a decreased intake of alcoholic beverages and tobacco smoking, would markedly lower the incidence of ESCC. From a public health standpoint, our study suggests that the greatest impact would come from decreasing consumption of alcoholic beverages, particularly among the 12.2% of the population who consume more than 60 g of alcohol per day. We expect that further studies on socioeconomic variables and diet will help to identify a new set of esophageal cancer risk factors that may be amenable to intervention.

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