

## Cigarette smoking and alcohol drinking and esophageal cancer risk in Taiwanese women

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**METHODS:** This is a multi-center, hospital-based, case-control study. Case patients consisted of women who were newly diagnosed and pathology-proven to have esophageal squamous cell carcinoma (ESCC) from three large medical centers (one from Northern and two from Southern Taiwan, respectively) between August 2000 and December 2008. Each ESCC patient was matched with 4 healthy women based on age (within 3 years) and hospital of origin, from the Department of Preventive Medicine in each hospital. A total of 51 case patients and 204 controls, all women, were studied.

**RESULTS:** Frequencies of smokers and drinkers among ESCC patients were 19.6% and 21.6%, respectively, which were significantly higher than smokers (4.4%) and drinkers (4.4%) among controls (OR = 4.07, 95% CI: 1.36-12.16,  $P = 0.01$ ; OR = 3.55, 95% CI: 1.03-12.27,  $P = 0.04$ ). Women who drank an amount of alcohol more than 158 g per week had a 20.58-fold greater risk (95% CI: 1.72-245.62,  $P = 0.02$ ) of ESCC than those who never drank alcohol after adjusting for other covariates, although the sample size was small.

**CONCLUSION:** Cigarette smoking and alcohol drinking, especially heavy drinking, are the major risks for developing ESCC in Taiwanese women.

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**Key words:** Esophageal squamous cell carcinoma; Taiwanese women; Cigarette smoking; Alcohol drinking

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### Abstract

**AIM:** To investigate the etiology of esophageal cancer among Taiwanese women.

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## INTRODUCTION

Esophageal cancer, predominately esophageal squamous cell carcinoma (ESCC), was the 9th leading cause of cancer deaths in Taiwan in 2006<sup>[1]</sup>. The age-adjusted mortality rate was 0.54 per 100 000 persons for females, much lower than for males (9.04 per 100 000 persons), due to low incidence rate of esophageal cancer in females (0.77 per 100 000 persons in females and 11.99 per 100 000 persons in males).

Most epidemiological studies, including ours, regarding the etiology of ESCC have been conducted in men or both combined genders<sup>[2-6]</sup>, but very few have only focused on the effect of risk/protective factors on esophageal cancer among women<sup>[7,8]</sup>. Cheng *et al*<sup>[7]</sup> conducted a population-based, case-control study in four regions in England and Scotland. They found that high body mass index in early adulthood and low consumption of fruit are the most important risk factors, but that breastfeeding may confer a protective effect, for esophageal adenocarcinoma<sup>[7]</sup>. In the same group led by Sharp *et al*<sup>[8]</sup>, the researchers found that cigarette smoking and consumption of hot food and tea are significant risk factors for ESCC in the same four regions of the previous study<sup>[7]</sup>. Since, in Taiwan, no study has examined the determinants of ESCC occurrence in women, we conducted a multicenter, hospital-based, case-control study to investigate this issue.

## MATERIALS AND METHODS

### Selection of cases and controls

Case patients were women who were newly diagnosed and pathology-proven to have ESCC from three large medical centers: National Taiwan University Hospital (NTUH) located in northern Taiwan, Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Veterans General Hospital located in southern Taiwan. These three hospitals are the main medical centers in their geographic areas and are accessible to patients from all socioeconomic groups in Taiwan. We matched each case patient with 4 healthy women based on their age (within 3 years) and hospital of origin, from the Department of Preventive Medicine. In total, 51 cases and 204 controls, all women, were recruited for interview between August 2000 and December 2008. During the same period, we recruited 530 male ESCC patients from these three medical centers. The study women were interviewed to collect demographic and substance use information by trained interviewers using a standardized questionnaire which was used earlier in an esophageal cancer study of

Taiwanese men<sup>[2,3]</sup>. This study was approved by the Human Subjects Committee of KMUH; informed consent was obtained from all subjects.

### Questionnaire

The information collected regarding substance-use habits included whether the subject had been a habitual areca chewer, cigarette smoker or alcoholic beverage drinker in her lifetime. Subjects who had smoked more than 10 cigarettes per week for at least 6 mo were defined as cigarette smokers. Those who reported regularly chewing betel quid for at least 6 mo were defined as areca chewers. For those who were cigarette smokers or areca chewers, the amount of consumed tobacco or areca per week was also collected. For alcohol drinking, subjects who had drunk beer, wine or distilled spirits more than once a week for at least 6 mo were defined as alcoholic beverage drinkers. For those who had ever consumed alcohol, detailed information was collected as to percentage of alcohol content (categorized as < 10%, 10%-19%, 20%-49%, and  $\geq$  50%) and number of alcohol drinks consumed per week. One drink was defined as a bottle or can of beer, a medium glass of wine, a small glass of port/sherry, or a nip of spirits/liqueur.

### Statistical analysis

Descriptive analysis was applied to demographic data to determine respective distributions. The averaged alcohol intake (in grams) per week for each type of beverage was estimated by multiplying the midpoint value for each intake frequency by the standard drink volume per week and median percentage of alcohol content (categorized as < 10%, 10%-19%, 20%-49%, and  $\geq$  50%). Unconditional logistic regression was used to assess the association between case/control status and use of substances (tobacco, alcohol, and areca) and other covariates. Data were analyzed using the SAS 9.1 statistical package; all *P*-values were two-sided.

## RESULTS

The distributions of age, tea consumption, and educational level were comparable between case patients and controls (Table 1). The frequencies of smokers, drinkers, and areca chewers were higher in case patients than in controls. After adjusting for other covariates, the status of smoking and drinking remained significant. Compared to non-smokers, smokers had a 4.07-fold (95% CI: 1.36-12.16, *P* = 0.01) greater risk of developing ESCC in women. Compared to non-drinkers, drinkers had a 3.55-fold (95% CI: 1.03-12.27, *P* = 0.04) greater risk of developing ESCC (Table 1). Since smoking and drinking alcohol are the significant risk factors for ESCC, we further examined their dose-response effect by dichotomizing the average amount of alcohol intake per week by the median (cigarette smoking: 3.5 packs/wk; alcohol drinking: 158 g/wk). We found that women who drank an amount of alcohol more than 158 g per week had a 20.58-fold greater disease risk (95% CI: 1.72-245.62, *P* = 0.02) than those who

**Table 1** Demographic characteristics and frequency of substance use in female esophageal squamous cell carcinoma patients and their controls (*n* = 255)

Variables	Cases ( <i>n</i> = 51) <i>n</i> (%)	Controls ( <i>n</i> = 204) <i>n</i> (%)	Crude OR (95% CI)	Adjusted OR <sup>1</sup> (95% CI)	<i>P</i> -value <sup>1</sup>
Age (yr)					
≤ 65	17 (33.3)	74 (36.3)	1.00	1.00	0.2467
> 65	34 (66.7)	130 (63.7)	1.14 (0.60, 2.18)	1.56 (0.70, 3.50)	
Educational level (yr)					
≤ 9	36 (70.6) <sup>2</sup>	179 (87.8)	1.00	1.00	0.0962
> 9	8 (15.7) <sup>2</sup>	25 (12.3)	1.59 (0.67, 3.81)	1.78 (0.68, 4.64)	
Tea consumption					
No	13 (25.5) <sup>2</sup>	37 (18.14)	1.00	1.00	0.1743
Yes	36 (70.6) <sup>2</sup>	167 (81.86)	1.63 (0.79, 3.37)	1.82 (0.78, 4.24)	
Areca chewing					
Non-chewers	48 (94.1)	203 (99.5)	1.00	1.00	0.4016
Chewers	3 (5.9)	1 (0.5)	12.69 (1.29, 124.61)	3.41 (0.13, 88.80)	
Smoking status					
Non-smokers	41 (80.39)	195 (95.59)	1.00	1.00	0.0107
Smokers	10 (19.61)	9 (4.41)	5.28 (2.02, 13.82)	4.07 (1.36, 12.16)	
≤ 3.5 pack/wk	6 (11.76)	4 (1.96)		6.08 (1.43, 25.94)	
> 3.5 pack/wk	4 (7.84)	5 (2.45)		2.09 (0.39, 11.23)	
Alcohol consumption					
Non-drinkers	40 (78.4)	195 (95.6)	1.00	1.00	0.0378
Drinkers	11 (21.6)	9 (4.4)	5.96 (2.32, 15.32)	3.55 (1.03, 12.27)	
≤ 158 gm/wk	3 (5.9)	8 (3.9)		2.06 (0.44, 9.63)	
> 158 gm/wk	8 (15.7)	1 (0.5)		20.58 (1.72, 245.62)	

<sup>1</sup>After adjusting for age (≤ 65 years *vs* > 65 years old), educational level (≤ 9 y *vs* > 9 yr), tea consumption (yes *vs* no), and status of smoking, areca chewing, and alcohol consumption (yes *vs* no); <sup>2</sup>We got missing data with the educational level and tea consumption of cases.

never drank alcohol after adjusting for age, educational level, cigarette smoking, and areca chewing. Women who drank less than 158 g per week had a slightly elevated risk of ESCC, but not significantly, compared to non-drinkers (Adjusted OR = 2.06, 95% CI: 0.44-9.63). In contrast, we did not find any significant dose-response effect of smoking on the risk of developing ESCC (Table 1).

## DISCUSSION

This multi-center hospital-based case-control study shows that cigarette smoking and alcohol drinking are the major risk factors for ESCC in Taiwanese women. The effect of alcohol drinking on ESCC risk is mainly confined to heavy drinkers (> 158 g/wk). Tobacco and alcohol are classified as class 1 carcinogens by the International Agency for Research on Cancer<sup>[9]</sup>. Although cigarette smoking and alcohol drinking are well-known risk factors for ESCC<sup>[10-15]</sup>, the majority of findings have been from studies among men.

To our knowledge, only two papers have been published which solely investigate the risk/protective factors of esophageal cancer in women<sup>[7,8]</sup>. Cheng *et al*<sup>[7]</sup> first conducted a multi-center, population-based, case-control study in four regions in England and Scotland. They collected 74 incident cases of women with histologically confirmed diagnoses of esophageal adenocarcinoma, and 74 female controls matched by age. They found that high body mass index in early adulthood and low consumption of fruit are important risk factors for esophageal adenocarcinoma. In contrast, breastfeeding may confer a protective effect, but this needs further confirmation as suggested by the authors<sup>[7]</sup>. In the same group

led by Sharp *et al*<sup>[8]</sup>, the researchers conducted another population-based, matched case-control study of histologically confirmed ESCC in women in the same four regions. There were 159 case-control pairs. They found that cigarette smoking and the consumption of hot food and tea are significant risk factors. However, they did not find that alcohol drinking was a significant risk factor for ESCC, a result which is different from our findings.

Tobacco contains numerous carcinogens and many studies have demonstrated its link to esophageal cancer<sup>[8,12-14,16-19]</sup>. In point of fact, the likelihood that cigarette smoking is more of a promoter than a mutagenic initiator is seen epidemiologically, as when heavy smokers stop smoking their risk of developing lung cancer is greatly diminished. Moreover, the most predominant chemicals in cigarette smoke are known promoters as they share mechanistic properties of known tumor promoters (i.e. they have threshold levels of action; they are reversible in action; their biological effects can be overridden by anti-tumor promoters, anti-oxidants and chemopreventive agents in the diet, *etc.*)<sup>[20-23]</sup>. However, for alcoholic beverages, it is not clear what exact mechanisms cause the increased risk of esophageal cancer. The commonest ingredient of all beverages is ethanol. Although ethanol has not been shown as carcinogenic in laboratory animals, it may act through its major metabolite, acetaldehyde, which is a carcinogen in animal models<sup>[24,25]</sup>. Alternatively, ethanol could exert a promoting effect by either solubilizing tobacco-specific carcinogens or enhancing their penetration into the esophageal mucosa to cause direct toxicity or oxidative damage on the epithelial mucosa<sup>[18,26]</sup>. In addition, alcoholic beverages may activate other carcinogenic compounds, such

as N-nitrosamines and urethane, to increase the risk of malignancies of the upper aerodigestive tract<sup>[9,17,26]</sup>.

A relatively small sample size was the major limitation in this study. Since the incidence rate of ESCC in Taiwanese women is extremely low (average 0.81 per 100 000 for the preceding 5 years), a large effort was made in this study to recruit all incident cases of ESCC from three medical centers in Taiwan. Because of small sample size, we are unable to investigate other factors, such as fruit and vegetable intake, which may have a modest protective effect on ESCC in women. In conclusion, our results suggest that cigarette smoking and alcohol drinking, especially heavy drinking, are the major risks affecting the development of ESCC in Taiwanese women.

## COMMENTS

### Background

Esophageal cancer, predominately esophageal squamous cell carcinoma (ESCC), was the 9th leading cause of cancer deaths in Taiwan in 2006. While most epidemiological studies regarding the etiology of ESCC have been conducted in men or both combined genders, very few have solely focused on the effect of risk/protective factors on esophageal cancer among women.

### Research frontiers

Since, in Taiwan, no study has examined the determinants of ESCC occurrence in women, the authors conducted a multi-center, hospital-based, case-control study to investigate this issue.

### Innovations and breakthroughs

The results of this study suggest that cigarette smoking and alcohol drinking, especially heavy drinking, are the major risk factors for developing ESCC in Taiwanese women.

### Applications

This study suggests that to abstain from smoking and drinking can prevent the development of ESCC in women.

### Peer review

This manuscript is a well-written article. It is a quite interesting study by mainly being held on women population. The authors investigated the etiology of esophageal cancer among women in Taiwan. It is a multi-center hospital-based case-control study which concluded that cigarette smoking and alcohol drinking, especially for heavy drinkers, are the major risk factors for developing ESCC in Taiwanese women.

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