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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INTRODUCTION
Esophageal cancer, predominately esophageal squamous cell carcinoma (ESCC), was the 9th leading cause of cancer deaths in Taiwan in 2006[1]. 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[2-6], but very few have only focused on the effect of risk/protective factors on esophageal cancer among women[7,8]. Cheng et al[7] 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[1]. In the same group led by Sharp et al[8], 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[7]. 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[2-3]. 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 either 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 ≥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 ≥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

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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. Although cigarette smoking and alcohol drinking are well-known risk factors for ESCC, a result which is different from our findings.

The commonest ingredient of all beverages is ethanol. 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.). However, for alcoholic beverages, it is not clear what exact mechanisms cause the increased risk of esophageal cancer.

To our knowledge, only two papers have been published which solely investigate the risk/protective factors of esophageal cancer in women[7,8]. Cheng et al. 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[8]. In the same group led by Sharp et al., 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[8,12-14,16-19]. 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.). 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[24,25]. 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[16,20]. 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\textsuperscript{9,17,26}. 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 4th 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.

**REFERENCES**

1. Cancer Registry Annual Report. National Department of Health, Taiwan, Republic of China, 2007. Available from: URL: http://www.bhp.doh.gov.tw/BHPINET/Portal/StatisticsShow.aspx?No=20091300001
2. Wu MT, Lee YC, Chen CJ, Yang PW, Lee CJ, Wu DC, Hsu HK, Ho CK, Kao EL, Lee JM. Risk of betel chewing for oesophageal cancer in Taiwan. Br J Cancer 2001; 85: 658-660
3. Enzinger FC, Mayer RJ. Esophageal cancer. N Engl J Med 2003; 349: 2241-2252
4. Lee CH, Lee JM, Wu DC, Hsu HK, Kao EL, Huang HL, Wang TN, Huang MC, Wu MT. Independent and combined effects of alcohol intake, tobacco smoking and betel quid chewing on the risk of esophageal cancer in Taiwan. Int J Cancer 2005; 113: 475-482
5. Morikawa Y, Miura K, Sasaki S, Yoshida K, Yoneyama S, Sakurai M, Ishizaki M, Kido T, Naruse Y, Suwazono Y, Higashiyama M, Nakagawa H. Evaluation of the effects of shift work on nutrient intake: a cross-sectional study. J Occup Health 2008; 50: 270-278
6. Knutsson A. Health disorders of shift workers. Occup Med (Lond) 2003; 53: 103-108
7. Cheng KK, Sharp L, McKinney PA, Logan RF, Chilvers CE, Cook-Mozaffari P, Ahmed A, Day NE. A case-control study of oesophageal adenocarcinoma in women: a preventable disease. Br J Cancer 2000; 83: 127-132
8. Sharp L, Chilvers CE, Cheng KK, McKinney PA, Logan RF, Cook-Mozaffari P, Ahmed A, Day NE. Risk factors for squamous cell carcinoma of the oesophagus in women: a case-control study. Br J Cancer 2001; 85: 1667-1670
9. Blot WJ. Alcohol and cancer. Cancer Res 1992; 52: 2119s-2123s
10. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer 2001; 85: 1700-1705
11. Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol 2006; 7: 149-156
12. Freedman ND, Abnet CC, Leitzmann MF, Mousseau T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol 2007; 165: 1424-1433
13. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. Semin Radiat Oncol 2007; 17: 2-9
14. Ishiguro S, Sasazuki S, Inoue M, Kurahashi N, Iwasaki M, Tsugane S. Effect of alcohol consumption, cigarette smoking and flushing response on esophageal cancer risk: a population-based cohort study (JPHC study). Cancer Lett 2009; 275: 240-246
15. Pandeya N, Williams G, Green AC, Webb PM, Whiteman DC. Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. Gastroenterology 2009; 136: 1215-1224, e1-e2
16. Wu IC, Lu CY, Kuo FC, Tsai SM, Lee KW, Kuo WR, Cheng YJ, Kao EL, Yang MS, Ko YC. Interaction between cigarette, alcohol and betel nut use on esophageal cancer risk in Taiwan. Eur J Clin Invest 2006; 36: 236-241
17. Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V, Varghese C, Boffetta P. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. Int J Cancer 2003; 105: 681-686
18. Castellsague X, Quintana MJ, Martinez MC, Nieto A, Sanchez MJ, Juan A, Monner A, Carrera M, Agudo A, Quer M, Munoz N, Herrero R, Franceschi S, Bosch FX. The role of type of tobacco and type of alcoholic beverage in oral carcinogenesis. Int J Cancer 2004; 108: 741-749
19. Wu M, Zhao JK, Hu XS, Wang PH, Qin Y, Lu YC, Jiang Y, Liu AM, Wu DL, Zhang ZF, Frans KJ, van ‘t Veer P. Association of smoking, alcohol drinking and dietary factors with esophageal cancer in high- and low-risk areas of Jiangsu Province, China. World J Gastroenterol 2006; 12: 1686-1693
20. Uppham BL, Weis LM, Rummel AM, Masten SJ, Trosko JE. The effects of anthracene and methylated anthracenones on gap junctional intercellular communication in rat liver epithelial cells. Fundam Appl Toxicol 1996; 34: 260-264
21. Thilly WG. Have environmental mutagens caused oncogene mutations in people? Nat Genet 2003; 34: 255-259
22. Trosko JE, Uppham BL. The emperor wears no clothes in the field of carcinogen risk assessment: ignored concepts in cancer risk assessment. Mutagensis 2005; 20: 81-92
23. Tai MH, Uppham BL, Olson LJ, Tsao MS, Reed DN Jr, Trosko JE. Cigarette smoke components inhibited intercellular communication and differentiation in human pancreatic ductal epithelial cells. Int J Cancer 2007; 120: 1855-1862
24. Blot W, McLaughlin J, Fraumeni JF. Esophageal Cancer. In: Schottenfeld D, Fraumeni J, editors. Cancer epidemiology and prevention. New York: Oxford University Press, 2006: 681-706
25. Harris EL. Association of oral cancers with alcohol consumption: exploring mechanisms. J Natl Cancer Inst 1997; 89: 1656-1657
26. Huang WY, Wynn DM, Brown LM, Gridley G, Bravo-Otero E, Diehl SR, Fraumeni JF Jr, Hayes RB. Alcohol concentration and risk of oral cancer in Puerto Rico. Am J Epidemiol 2003; 157: 881-887

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