The carcinogenetic impact of risk factors on esophageal cancer (EC) may differ according to the portion of the esophagus where the tumor occurs. It is unclear why more esophageal squamous cell carcinomas (SCC) developed in the middle location. We carried out a multicenter case-control study in Taiwan to assess anatomical subsite risk discrepancy for this neoplasm in regard to the consumption of alcohol, tobacco and betel quid. Four hundred forty seven incident patients with pathology-proven SCC of the esophagus (107 were upper-third [U/3-EC], 199 middle-third [M/3-EC] and 141 lower-third [L/3-EC] cases), as well as 1,022 gender, age and study hospital matched controls were analyzed by unconditional ordered polytomous logistic regression. All consumption of the three substances was related to the development of each subsite of EC, with a heterogeneously higher risk for current smokers (adjusted odds ratio (AOR) = 6.2) found in M/3-EC and for current drinkers in U/3-EC (AOR = 4.9). The joint risk of contracting lower two-third EC for drinking and smoking appeared to significantly surpass those estimated by a multiplicative interaction model. Concomitant exposure to these two agents brought the risks of EC at all three subsites up to 10- to 23.9-fold and additionally activated risk and, further, that these agents may also have combined effects produced synergistically with the genesis of EC.12-14 Nevertheless, whether their carcinogenetic impact differs according to the portion of the esophagus where the tumor occurs remains unknown. The purpose of this multicenter case-control study is, therefore, to clarify the anatomical subsite discrepancies in regard to the effects of the three agents on the development of EC.

Material and methods

Selection of cases and controls

This is a large-scale collaborative case-control study established in three medical centers located in northern Taiwan.
(National Taiwan University Hospital (NTUH), Taipei) and southern Taiwan (Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Veterans General Hospital (KVGH), Kaohsiung). These hospitals provide comprehensive medical services to patients of each socioeconomic situation. The detail study design for this investigation has been described previously. In brief, however, we studied newly diagnosed cases of SCC of the esophagus (ICD-9, code 150) for those hospitalized in the Department of Chest Surgery and the Department of Gastroenterology at these three hospitals. Cases were identified through a system of rapid case recognition, recording selected demographic characteristics and related medical records, so that the patients could be identified and selected for our study as soon after diagnosis as possible. All suspected cancer cases were verified by histological materials, and only patients who have consistently been histologically confirmed to have esophageal SCC by the study pathologists were included.

Diagnostic images, including x-rays, MRI, CT scan and endoscopy, were extracted and used for the identification of tumor location occurring in the esophagus. Based on the criteria employed by the National Cancer Institute’s SEER program, cancer lesion at the anatomical subsite of the esophagus was determined according to the characteristic location that the tumor occurred, with distances measured from the midincisors as follows: (1) upper-third (U/3-EC), from the cricopharyngeal sphincter (15 cm) to the tracheal bifurcation (23 cm); (2) middle-third (M/3-EC), from 23 cm to the approximate level of the T9 vertebral body (32 cm); and (3) lower-third (L/3-EC), from 32 cm to the gastroesophageal junction (40 cm). Between 1996 and 2004, we recruited 546 histologically proven incident patients with EC. Among them, 107 cases were diagnosed with U/3-EC, 199 with M/3-EC, 141 with L/3-EC, 10 with U/3+M/3-EC, 35 cases with M/3+L/3-EC and 19 with no available formation on the anatomical subsite. The remaining 35 cases had missing data, in regard to the variables studied. To focus the evaluation on the subsite-specific effect in the final analyses, we included only 447 patients who had simply one subsite of cancer lesion.

The control subjects were recruited from the same hospitals. A system for the recognition of background data for hospitalized patients was developed and established in the Department of Preventive Medicine at each hospital. Community residents who were 1-day hospitalized in these departments for their routine physical checkup at the first visit were considered eligible controls. Subjects 25 years of age or older that were confirmed to be without malignant tumors were contacted and invited to be our controls. Within 4 weeks after each esophageal carcinoma patient was identified, 1–2, or rarely, 3 eligible controls were selected and matched to each case, in terms of the study hospital, gender and age (±3-years). A total of 1,022 controls were successfully interviewed. Of those, 918 subjects were matched to the cancer patients (447 cases) who had purely 1 anatomical subsite of cancer lesion. To obtain more robust findings, sensitivity analysis was performed and assessed in 2 series of controls. Similar results were found for the inclusion of all controls (1022 subjects) and of those (918 subjects) matched to the analyzed cases, with better precision of risk estimates in the former control group. The results from all controls analyses were presented.

Data collection

This study was reviewed and approved by the Institutional Review Boards of National Taiwan University Hospital and Kaohsiung Medical University Hospital. All participants gave written, informed permission to be interviewed and for the tracing of their medical records. Participants were interviewed by well-trained interviewers using a standardized questionnaire to draw out detailed information on demographic characteristics, substance use and daily diet.

Alcohol drinkers, tobacco smokers and betel quid chewers were defined separately as subjects who had consumed any alcoholic beverage ≥1 times per week, had smoked ≥10 cigarettes per day and had chewed ≥1 betel nut (measured as quid) per day for at least 6 months. Among them, current users were those who had practiced any of these habits within a 1-year period before the interview; former users were defined as those who had stopped any of the habits for at least 1 year prior to diagnoses or interviews. The information about substance use was collected with regard to the age of commencement, daily consumption, duration of the use and the type of substance consumed. For betel quid chewers, additional information was collected as to the types of substances consumed with the areca nut, which in Taiwan is usually a piece of betel leaf, stem, or inflorescence of Piper Betel Linn, or mixed. Nevertheless, not all types of betel quid products use tobacco as an ingredient. To assess the risk of the total alcohol intake, data on the types of alcoholic beverage (beer, wine, whisky, brandy, Taiwanese rice wine, Chu Yeh Ching liquor and Kaoliang spirit), the amount of ethanol consumed for each type of beverage (according to the ethanol content of each beverage and the total amount consumed), the number of drinks per day and the average frequency per week was converted to the total consumption of alcohol in grams per day. Since beer is the most popular alcoholic beverage in Taiwan, 1 drink was referred as consuming 15.75 g of alcohol, which equates to 1 regular bottle (350 ml) of beer containing 4.5% ethanol. To investigate the effect of cumulative lifetime exposure, the number of “bottle × years” and “pack × years” was calculated by multiplying the amount of the substances consumed, 15.75 g-alcohol bottles per day drunk, 20-cigarette packs per day smoked or 10-betel quid packs per day chewed, by the years of the substance used. Daily dietary habits were assessed by measuring the consumption of 20 food groups according to 3 time periods (<20, 20–40 and >40 years of age). Food intake questions were directed at the frequency and quantity for each time period. Only the consumption of the latest period for each patient was used for the data analyses.

Statistical analyses

The association between cancer at the upper, middle and lower-third of the esophagus and the respective alcohol consumption, cigarette smoking and betel quid chewing were examined simultaneously using unordered polytomous logistic regression, which allows for statistical modeling of a dependent variable with more than 2 categories. In such models, 3 sets of coefficients were separately produced by the maximum likelihood method in order to compare each tumor subsite with the controls. The odds ratio (OR), as an approximation of the relative risk, was generated by exponentiating these coefficients. To evaluate the capacity of a given risk factor to distinguish the risk of contracting EC at different subsites, the heterogeneity in the ORs between two tumor locations was assessed using the OR ratio calculated by the exponentiation of the corresponding two coefficients. However, only the largest difference in OR ratio was displayed. All regression models contained the matched factors, such as the study hospital (NTUH, KMUH and KVGH), gender and age (<41, 41–50, 51–60, 61–70 and >70 years old), the potential confounding variables, including the years of schooling (<7, 7–12 and >12 years of education), consumption of fruits (No, 1–7, 8–14 and >14 times per week) and of vegetables (No, 1–7, 8–14 and >14 times per week) and, where appropriate, the use of other substances as covariates. The dose-response linear trend across increasing categories of substance use was examined by assigning the median for each exposure category and treating the categories as a continuous variable. The departure from OR multiplicativity was assessed by fitting polytomous logistic regression models containing binary categorical variables, as well as their cross-products. The final model used for interpreting the summary results was assessed for the overall fit using the Hosmer–Lemeshow goodness-of-fit (GoF) test for separate pairs of logistic models.

Results

Cancer cases of the upper, middle and lower-third of the esophagus, as well as the controls studied, were generally comparable with regard to the hospital, gender, age and ethnicity. However,
The ORs and OR ratios were adjusted for age, gender, study hospital, education, consumption of vegetables and fruits, pack × years of cigarette smoking and of betel quid chewing.  

Values in parentheses are 95% CI values.  

The ORs and OR ratios were adjusted for age, gender, study hospital, education, consumption of vegetables and fruits, pack × years of cigarette smoking and of betel quid chewing.  

The distribution of three types of substance use is presented in Table I. In contrast to having the habit of betel quid chewing, an overwhelming majority of EC patients had the habit of drinking or
greater cancer risk (adjusted OR 2.1–11.7 for U/3-EC and 2.1–12.2 for L/3-EC, respectively). However, varied subsite-specific risks across the three portions of the esophagus were not observed to be significant (OR ratios for the highest OR in M/3-EC compared with the lowest OR in L/3-EC were 0.9- to 1.6-fold, p > 0.05). A linear dose-response relationship was detected for time and intensity-related aspects of alcohol intake. All types of alcoholic beverages were associated with an increased risk of EC.

Table III uses tumor subsites to display the risk of contracting EC from tobacco smoking. Current-smokers were observed to have a more than 2.5-fold elevated risk of EC than nonsmokers, with the highest risk found in the portion of the middle third. A more steep increase in risk, with respect to the length of the time...
of tobacco consumed, was detected among M/3-EC patients than among cancer patients at the other locations. Further, subsite heterogeneity in cancer risk between M/3-EC and L/3-EC was linked to the exposure of tobacco smoke for >30 years (OR ratios > 2.3–3.2). Smokers who inhaled the tobacco experienced a higher risk of EC than noninhaling smokers, and this was observed in all anatomical subsites.

The diverse subsite-specific effects of areca nut chewing on EC are presented in Table IV. Compared to nonchewers, a higher risk of EC than non-inhaling smokers, and this was observed in all anatomical subsites. The joint risk (adjusted OR = 23.3) for drinkers who smoked appeared to significantly surpass the risk (expected OR = 3.4) predicted from the product of the risk of each factor acting separately (GoF test, p > 0.05). As compared to nonsmokers of any type of substances, betel quid chewers had a 4.7-fold elevated risk of contracting U/3-EC, and the risk was significantly higher than that (OR = 2.1) for M/3-EC (OR ratio = 2.2). A combined use of alcohol and tobacco was linked to a >10-fold risk for the development of cancer lesion at each location. Further, as compared to that in L/3-EC, a heterogeneously greater joint effect from drinking and smoking was observed in M/3-EC. The greatest risk of

### Table V – Multiplicative Interaction Effects of Alcohol Intake, Cigarette Smoking and Betel Quid Chewing on Esophageal Cancer Arranged by the respective anatomical subsite of the esophagus, Taiwan, 1996–2004

| Factors | Upper AOR | Middle AOR | Lower AOR |
|---------|-----------|------------|-----------|
| Alcohol intake/cigarette smoking³ | | | |
| Never/never | 16 | 18 | |
| Never/ever | 20 | 15 | |
| Ever/never | 4 | 6 | |
| Ever/ever | 159 | 102 | |
| Alcohol intake/betel quid chewing⁴ | | | |
| Never/never | 32 | 31 | |
| Never/ever | 4 | 2 | |
| Ever/never | 83 | 48 | |
| Ever/ever | 80 | 60 | |
| Cigarette smoking/betel quid chewing⁶ | | | |
| Never/never | 19 | 23 | |
| Never/ever | 1 | 1 | |
| Ever/never | 96 | 56 | |
| Ever/ever | 83 | 61 | |

Values in parentheses are 95% CI values.

Expected OR, predicted from the product of the risk for each factor acting separately. Wald Z-tests for cross-product terms based on a multiplicative model. Odds ratios were adjusted for the daily alcohol intake and covariates.

### Table VI – Adjusted Odds Ratios for Esophageal Cancer Associated with Combined Use of Alcohol Tobacco and Betel Quid Arranged by the respective anatomical subsite of the esophagus, Taiwan, 1996–2004

| Factors | Upper AOR | Middle AOR | Lower AOR |
|---------|-----------|------------|-----------|
| Nondrinker/nonsmoker/nonchewer | 1.0 | 1.0 | 1.0 |
| Betel quid chewing | | | |
| Chewer | 4.7 (2.7–8.3) | 2.1 (1.4–3.3) | 3.0 (1.8–5.0) |
| OR ratio for chewer² | 2.2 (1.2–4.0) | 1.4 (0.8–2.4) | |
| Alcohol intake/betel quid smoking | | | |
| Nondrinker/Smoker | 2.5 (0.9–6.5) | 2.4 (1.1–5.1) | 1.3 (0.6–2.8) |
| Drinker/Non-smoker | 1.2 (0.3–6.2) | 1.4 (0.4–4.5) | 1.6 (0.6–4.4) |
| Drinker/Smoker | 15.9 (6.6–38.1) | 23.9 (12.4–45.9) | 10.0 (5.3–18.9) |
| OR ratio for drinker/smoker³ | 1.6 (0.6–4.4) | 2.4 (1.0–5.6) | 1.0 |
| Alcohol intake/betel quid chewing/betel nut chewing | | | |
| Drinker/smoker/chewer | 73.0 (29.8–188.7) | 50.8 (25.0–103.3) | 30.3 (15.2–60.4) |
| OR ratio for drinker/smoker/chewer³ | 2.5 (0.9–7.1) | 1.7 (0.7–4.1) | 1.0 |

Values in parentheses are 95% CI values.

³Odds ratios were estimated from the model that includes the binary indicators for chewing, drinking, smoking and the cross-product of drinking and smoking, as well as the covariates of age, gender, study hospital, education, consumption of vegetables and fruits. The OR for the middle-third of the esophagus was the reference group. The OR for the lower-third of the esophagus was the reference group.
cancer for all 3 segments of the esophagus was consistently detected among patients who practiced the 3 habits simultaneously.

Discussion

This study presents evidence that consumption of alcohol, tobacco and, to a lesser extent, betel quid, was closely related to the genesis of esophageal SCC at different anatomical subsites. While alcohol intake was found to affect the esophagus with a nondiscrepant risk of contracting M/3-EC and U/3-EC, respectively, than those of contracting cancers at other subsites.

Alcohol abuse has been known to be involved in the pathogenesis of EC.3 Although the independent risk of this agent on the occurrence of this neoplasm has been verified among nonsmokers,20 there is limited information to date about its carcinogenetic impact on anatomical subsites of the esophagus. Studies conducted in Japan3 and China4 have reported that drinking was associated with an elevated risk of contracting M/3-EC and U/3-EC, respectively, than those of contracting cancers at other subsites.

Concerns about the location effect of tobacco use on EC have been examined in several case–control studies.3–5,10 A comparatively higher risk was consistently claimed for cancers occurring in the middle portion than at the other portions in two Asian studies.3,4 As compared to the risk for L/3-EC, our study further demonstrates that smokers had a significantly greater likelihood of producing M/3-EC as a result of tobacco exposure for at least 30 years (OR ratio = 2.3–3.2). While reports from one Indian study showed similar findings, the risk was associated to the smoking of bidi, a common tobacco product used locally.7 The esophagus receives most of its blood from the aorta and drains it to the liver and venal cava. The upper and lower-thirds of the esophagus are, respectively, supplied by the inferior thyroid artery and branches of the left gastric artery, and they are smaller than the branches from descending thoracic aorta, which supply to the middle-third of the esophagus.7 The stronger risk observed in M/3-EC might be related to more abundant blood supply in this area, thus increasing the action of tobacco carcinogens in this location.

Betel quid is typically prepared using a combination of areca nut, tobacco, inflorescence, the leaf and stem of the Piper Betel Linn and slaked lime. While the major ingredients are comparatively consistent, there is a geographic variation in the chewing of betel quid among different countries and different regions within them.22 Alkaloid arecoline, a major component in areca nut, is its most active ingredient. Experimental evidence from in vitro studies has shown that at least 4 N-nitrosamines, two of which are carcinogens, are produced from areca alkaloids during the chewing of betel quid.23 The Piper Betel Linn inflorescence, another important and aromatic flavored ingredient frequently added to the areca nut products in Taiwan, contains a high concentration of safrole (15.35 mg/g).24 Genotoxic effects of betel-specific safrole on tissues from oral and EC patients have been demonstrated.25,26

In certain areas of the Indian subcontinent and Southeast Asia, where betel quid chewing was identified as being a significant risk factor for EC,14,22,27,28 areca nut was habitually chewed mixed with tobacco. In contrast, studies conducted in Taiwan13 and South India14 reported that an increased cancer risk is associated with the consumption of betel quid without the addition of tobacco. In this study, we further uncovered the heterogeneity in risk in relation to the chewing tobacco-free betel quid among different tumor subsites of the esophagus, that a substantially higher risk for U/3-EC in contrast with M/3-EC was linked to prolonged exposure to betel quid (>20 years of chewing, OR ratio = 2.5). Similar heterogeneous risks were noticed among the chewers who consumed areca nut with a piece of Piper Betel Linn inflorescence in it. Such chewers had the highest elevated risk (OR = 8.0); this is lower than the significantly strong risk (OR = 11.6–13.5) found for oral and pharyngeal cancers and greater than the nonsignificantly moderate risk (OR = 2.9) observed for laryngeal cancer,15,16 for developing U/3-EC in our study. As a consequence of chewing and swallowing, parts of the areca juice and like contents can flow through to the esophagus, with the upper portion being the location where the juice is first in contact with. A typical picture of betel stains in the esophagus is shown in Figure 1, which was taken from an endoscopic exam for a regular chewer. –1 A piece of betel leaf remains. –2 Betel stains remains. –3 A case of severe (Barrette’s) esophagitis can be seen here.

FIGURE 1 – A typical picture of betel stains over the (A) upper (B) middle or (C) lower-third of the esophagus taken from an endoscopic exam for a regular chewer. –1 A piece of betel leaf remains. –2 Betel stains remains. –3 A case of severe (Barrette’s) esophagitis can be seen here. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
tobacco chewing was greater than the sum of the risk for each formed in regions with a high incidence rate of EC in India, pro-
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