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# Carcinogenetic impact of alcohol intake on squamous cell carcinoma risk of the oesophagus in relation to tobacco smoking

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ABSTRACT

Consumption of alcohol and tobacco, separately or jointly, can increase the risk of oesophageal squamous cell carcinoma (OSCC). It is unclear whether the amount of alcohol consumption by individual drinkers affects the joint carcinogenetic action of both agents. To demonstrate how the intensity of alcohol intake determines the risk of OSCC in relation to tobacco smoking, we conducted a multicentre case-control study. A total of 652 patients with pathology-proven OSCC, as well as 1127 gender, age, and study hospital matched controls were recruited. To identify a possible curvature in the continuous relationship between exposure and risk, we applied the generalised additive models to the collected data. Both non-drinkers who smoked tobacco and non-smokers who drank heavy alcohol (>30 g/day) were observed to have elevated cancer risks. A smoking habit-specific, non-linear increase in oesophageal cancer risk was recognised. Tobacco was found to interact with light-to-moderate alcohol (0.1–30 g/day) to increase the risk of oesophageal cancer in a supra-multiplicative way (Odds ratio (OR) ratio = 5.5–5.7, $p < 0.05$), whereas with heavy alcohol consumption in a simple multiplicative model (OR ratio = 1.7–2.3, $p > 0.05$). Weekly intake frequency had the strongest influence on the risk of neoplasm development. Alcohol consumption was responsible, respectively, for 18% and 77% of nonsmoking and smoking

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OSCC cases in this population. In conclusion, both light-to-moderate and heavy alcohol intake interact separately with tobacco in differently synergistic processes that can determine the development of this type of cancer.



## 1. Introduction

Heavy alcohol consumption has been demonstrated to be a major health hazard.[1] However, the consumption of light-to-moderate amounts of alcohol may not be detrimental, and may even be beneficial to the prevention of coronary heart disease and stroke.[2,3] Still, the effects of low-to-moderate alcohol consumption on other diseases, such as cancer, have not been well established.

Consumption of alcohol and tobacco, separately and together, are two of the most important determinants of carcinoma of the oesophagus.[4,5] Most studies have recognised that the combined effect of these two agents is more than additive, and this is often illustrated adequately by a simple multiplicative model.[6] However, evidence of supra-multiplicative interaction has been discovered in some earlier reports.[7,8] While ethanol itself has not been found to cause cancer in animal experiments,[4] it is, in general, considered either as a solvent for other active carcinogens, or as an enhancing factor.[4] It is uncertain whether the level of ethanol to which a subject is exposed might affect such joint carcinogenetic action.

Among men in Taiwan, the age-standardised incidence rate has been reported as 8.7 per 100,000 by the population-based cancer registries in 2002;[9] this is compatible to numbers found in intermediate and high-risk areas of central Europe and South America.[10] In regions such as northern France[11,12] and northern Italy,[13,14] where heavy alcohol intake is common, it is difficult to evaluate the effect of light-to-moderate alcohol consumption on oesophageal cancer. In Taiwan, where heavy alcohol consumption is less common, lifestyle and dietary factors may differ from those of the western populations.[15] Therefore, those special epidemiological characteristics warrant further research regarding the effects of alcohol consumption upon the genesis of oesophageal carcinoma within the Taiwanese population.

In the evaluation of dose-response relationship between alcohol intake and oesophageal cancer risk, categorical analysis, which assumes the risk is constant inside each category, was widely employed in earlier studies that modelled such associations.[16] Log-linear dependence, i.e. a proportional increase in log-risk in these models, was presumed. However, as with most biological measures, a non-linear effect of alcohol on cancer risk could be expected.[17] Further, data categorisation might induce some potential biases in the step function analysis.[18,19] In the process of looking for a possible curvature in the continuous relationship between exposure and risk, we employed the technique of generalised additive models (GAM), which assumes that the mean of the dependent variable depends on an additive predictor through a non-linear link function.[20]

The objectives of this study are 2-fold: first, to explore the carcinogenetic impact of different aspects of alcohol intake on the development of oesophageal cancer in relation to tobacco consumption, and second, to employ a more flexible approach (GAM) to the study of the dose-dependent relationship between the intensity of alcohol consumption and the risk of this neoplasm.

## 2. Patients and methods

### 2.1. Cases and controls

This multicentre case-control study was initiated in 1996 by National Taiwan University Hospital (NTUH) in northern Taiwan, and was extended in 2000 to include two medical centres in southern Taiwan: Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Veterans General Hospital (KVGH). These hospitals provide comprehensive medical services to patients of various socioeconomic levels.

The detailed study design for this investigation has been described previously.[8] In brief, a survey network for rapid case recognition and ascertainment was established among these three hospitals so that new oesophageal cancer cases could be identified and recruited into our study as soon as the diagnosis was confirmed. The study cases (primary invasive cancer of the oesophagus, ICD-9 150), were incident cancer patients recruited from the Department of Chest Surgery and the Department of Gastroenterology at these three hospitals from 1996, or 2000 to 2005. All of the cases have been histologically confirmed to have squamous cell carcinoma of the oesophagus by the endoscopists, surgeons or pathologists. Among the 802 pathology-proven cases, 652 patients (600 men and 52 women) were included in this study. Of those, more than half (51.7%) of the study cases with response rate of 71.5% were recruited from NTUH, and the rest with response rate of about 95% came from KMUH (21.9%) and KVGH (26.4%). Cancer patients excluded from this analysis were those who underwent a surgery then cannot participate ($n = 64$), those who had been discharged by the time we visited the wards ($n = 48$), and those who refused to be interviewed ($n = 38$). The distribution between the included and excluded cases was comparable with regard to age and gender ($\chi^2$ tests, $p > 0.05$). No substantial dissimilarity in the major variables explored was identified across the studied hospitals. All study patients were interviewed within 1 week of their diagnosis.

The control subjects were recruited from the same hospitals. Community residents older than 25 years who were one-day hospitalised in the Department of Preventive Medicine for their routine physical checkup at the first visit were identified as potential controls. From a list of all potential controls, we selected one to three controls (rarely, three controls) that matched each cancer patient in regard to gender, age (within 3-years) and hospitalisation (within 4 weeks after each case was identified). Of the 1187 matched controls, 1127

subjects (1038 men and 89 women) agreed to be interviewed and were recruited as the control group. Others refused to be part of the control group because they did not wish to be disturbed. The NTUH, KMUH and KVGH recruited, respectively, 52.6%, 21.1% and 26.3% of the controls.

### 2.2. Data collection

This study was approved by the Institutional Review Boards of NTUH and KMUH. A written, informed consent for the interview and for tracing medical records was obtained for both cases and controls. The interviews were carried out by well-trained staff members using a standard questionnaire, gathering information on demographic and socioeconomic characteristics, habits in regard to alcohol consumption, lifetime consumption of tobacco and betel quid, along with clinical histories and daily diets were collected from cases and controls.

There are a variety of alcoholic beverages conventionally consumed in Taiwan. According to the ethanol contained, these were primarily categorised into four classes:

(1) Beer-related beverages (containing 4.5–8% ethanol), including beer (4.5%), Palyta B (8%), and Vespi (8%). The latter two are types of light alcoholic beverages made with Chinese herbal medicine.
(2) Wine-related beverages (containing 12–16% ethanol), including fruit wine (12%), and Shaohsing wine (15%) fermented from glutinous rice and sake (16%).
(3) Liquor (containing 22–46% ethanol), including Taiwanese rice wine (22%), whisky (41%), brandy (41%), ginseng antler medical liquor (28%), Chu Yeh Ching liquor (45%), and Wu Chia Pee liquor (46%). The latter three are liqueurs produced with some Chinese medicinal herbs.
(4) Hard liquor (containing 55–65% ethanol), including Kaoliang (58%), Moutai (55%) and Da Qu spirits (65%).

Alcohol drinkers were defined as participants who had consumed any of the previously noted alcoholic beverages at least once per week for a minimum of 6 months. Ex-drinkers were those who had stopped drinking for at least 1 year prior to the interviews. The intake of ethanol in grams-per-drinking-day was estimated by multiplying the average total amounts of beverage drunk in a drinking day by the ethanol content contained in each type of beverage. The mean amount of ethanol consumed per day was derived by dividing the product of the intake frequency per-week and alcohol consumed per-drinking-day by seven. To investigate the effect of cumulative lifetime alcohol exposure, the number of 'drink × years' was calculated by multiplying the amount of alcohol per day consumed, measured as drinks (one drink corresponds to 15.75 grams of pure alcohol, which equates to one 350 ml of beer containing 4.5% ethanol) by the years of the substance used. The type of alcoholic beverage that was primarily consumed by each subject was employed by assessing its link with the risk of contracting oesophageal cancer.

Information on daily use, age of commencement and duration of tobacco smoking and/or of betel quid chewing was collected. Tobacco smokers and betel quid chewers were defined separately as subjects who had smoked ten or more cigarettes and had chewed one or more betel nut (measured as quid) per day for at least 6 months. The number of 'pack × years' was calculated by multiplying the amount of the substances consumed per day (20-cigarette packs per day for smoking or 10-betel quid packs per day for chewing) by the years of the substance used. Dietary habits were assessed by measuring the consumption of 20 food groups according to three time periods (younger than 20, 20–40, and over 40 years of age.) The frequency and quality of food consumption for each time period were obtained. Only the consumption of the latest period for each patient was used for the data analyses.

### 2.3. Statistical analysis

Unconditional multiple logistic regression models were employed for the categorical analysis.[21] The relationship between alcohol consumption and oesophageal cancer was measured by use of the odds ratio (OR), as an approximation of the relative risk, and by its corresponding 95% confidence intervals (CI). All regression equations included the matched factors (MF), i.e. gender, age (as a continuous variable) and the hospital of study, as covariates. In addition, covariates including their level of education (<7, 7–12, >12 years of schooling), lifetime betel quid chewing (Never, 1–10, 11–20, >20 pack × years), consumption of vegetables (<7, 7–14, >14 times per week) and of fruits (<7, 7–14, >14 times per week), and, where appropriate, cumulative tobacco smoking (Never, 1–20, 21–40, >40 pack × years) were adjusted in the multivariate models. Departure from OR multiplicativity was evaluated by fitting logistic regression models including indicator variables for levels of alcohol intake and tobacco smoking, as well as their cross-products. The OR ratio (smokers versus non-smokers) calculated by exponentiating the coefficient of the corresponding cross-product term in the interaction model was used to evaluate the capacity of smoking to distinguish the risk of contracting oesophageal cancer at different exposure levels of drinking.

To avoid modelling assumptions and prevent model misspecification, the GAM,[20] a nonlinear modelling method, was employed to explore the possible curve for the dose-response relationship between the consumption of alcohol and oesophageal cancer risk. In the GAM, an additive term, $f_j$ (X), estimated from smoothing operations was used to address the nonlinear relationship between the logit-transformed binary response and the continuous predictor. In this study, the nonparametric functions of locally-weighted running-line smoothers (*loess* function in S-plus)[22] were used to fit the GAM. In such models, nonparametric curves were estimated iteratively, cycling through all predictors by the method of backfitting until the optimal multivariate fit was reached. Sensitivity analysis on the span width of *loess* smoothing was performed to determine the appropriate window span. The weighted window span of 50% was used to model the function of all predictors. Significance of the nonlinear terms was tested by nonparametric $\chi^2$ tests.

In the analyses, separate modelling was performed for non-smokers and smokers. The final fitted GAM were: $\text{logit}(\text{P}) = \alpha_0 + f_1(\text{Drinking}) + \beta_1 \times (\text{Chewing}) + \sum \beta_j \times (\text{MF}_j) + \sum \beta_k \times (\text{C}_k)$ for non-smokers, and $\text{logit}(\text{P}) = \alpha_0 + f_1(\text{Drinking}) + \beta_1 \times (\text{Smoking}) + f_2(\text{Chewing}) + \sum \beta_j \times (\text{MF}_j) + \sum \beta_k \times (\text{C}_k)$ for

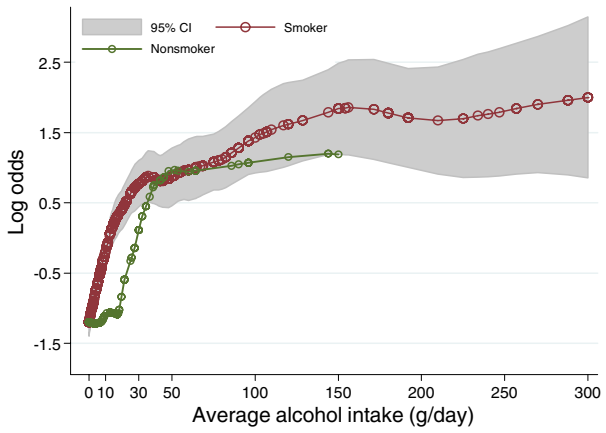


**Fig. 1 – Adjusted smooth relationship, derived from generalised additive models with 50% of weighted window span, of predicted log odds and average alcohol intake for non-smokers and smokers, respectively.**

smokers. For both models, $\alpha_0$ is the intercept; MF and C are, separately, the matched factors and covariates (education and consumption of vegetables and fruits) that we wanted to adjust for, and smoking and chewing were measured in continuous pack × years. To visually compare the relationship of cancer risks and daily alcohol consumption between non-smokers and smokers, the smoothing curve obtained from GAM for non-smoker was shifted to the position where the intercept of this model is the same as that for smokers (Fig. 1).

The proportion of oesophageal cancer cases attributable to all or one-specific level of alcohol intake (population attributable risk percent; PAR%) was calculated according to the approach of Bruzzi et al.[23] This method provides adjusted PAR% estimates by combining the adjusted OR estimates and the observed prevalence of risk factor among the case patients. All analyses were conducted using the statistical packages of Stata[24] and S-plus.[22]

## 3. Results

The cases and controls were generally comparable with regard to study hospital, gender, ethnicity and other background demographic factors. The age patterns were well matched in the two groups (Table 1). As compared to the control subjects, the cancer patients tended to be less educated (data not shown).

**Table 1 – Distribution of oesophageal cancer cases and controls associated with characteristics of selected demographic factors and consumption of alcohol and tobacco, Taiwan**

| Factors/Category | Cases ($n$ = 652) | Controls ($n$ = 1127) |
|---|---|---|
| Gender, % | | |
| Female | 8.0 | 7.9 |
| Male | 92.0 | 92.1 |
| Age (years), % | | |
| <45 | 10.3 | 8.8 |
| 45–54 | 23.5 | 26.5 |
| 55–64 | 27.8 | 26.5 |
| 65–74 | 23.3 | 25.7 |
| >74 | 15.2 | 12.4 |
| Mean ± SD[a] | 60.3 ± 12.0 | 60.0 ± 11.7 |
| Alcohol consumption | | |
| Non-drinking, % | 21.2 | 71.8 |
| Ever-drinking, % | 78.8 | 28.2 |
| Average amount of alcohol consumed per day, grams[a] | 67.6 ± 80.3 | 27.6 ± 43.0 |
| Alcohol amount contributed, grams/day (%) | | |
| Beer | 19.0 (28.2%) | 10.3 (37.5%) |
| Wine | 4.7 ( 6.9%) | 1.1 ( 3.9%) |
| Liquor | 24.9 (36.8%) | 9.6 (34.8%) |
| Hard liquor | 19.0 (28.1%) | 6.6 (23.8%) |
| Average amount of alcohol consumed per drinking day, grams[a] | 80.9 ± 85.1 | 54.7 ± 78.9 |
| No. of days per week alcohol consumed[a] | 5.5 ± 2.1 | 3.6 ± 2.1 |
| Years of alcohol consumption, year[a] | 31.7 ± 12.9 | 28.1 ± 13.6 |
| Total lifetime alcohol consumption, drink × year[b] | 135.7 ± 182.9 | 49.4 ± 84.1 |
| Tobacco consumption | | |
| Non-smoking, % | 14.4 | 57.2 |
| Ever-smoking, % | 85.6 | 42.8 |
| Average amount of cigarette smoked, cigarettes/day[a] | 22.1 ± 11.8 | 20.2 ± 11.8 |
| Years of cigarette smoked, year[a] | 36.4 ± 12.0 | 32.6 ± 13.7 |
| Total lifetime cigarette consumption, pack × year[b] | 40.3 ± 25.5 | 33.1 ± 23.4 |

a Measured in mean ± SD (SD: Standard deviation).
b Cumulative lifetime exposure (mean ± SD): One drink intake corresponds to 15.75 grams of alcohol and one smoking pack corresponds to 20 cigarettes.

The characteristics of consumption of alcohol and cigarette among oesophageal cancer cases and controls are presented in Table 1. Compared to the control subjects, the overwhelming majority of cancer patients had a history of alcohol consumption (78.8%) and tobacco smoking (85.6%). Among ever-drinkers, the average amount of alcohol consumed per-day, or per-drinking-day, the frequency, the years of drink and the lifetime alcohol intake for oesophageal cancer patients were all higher than their control-group counterparts. Similar findings for the amount- and the time-related features of tobacco smoking were observed among ever-smokers. In terms of average quantities of daily alcohol intake, the major alcoholic beverage for the control group was beer (37.5%), whereas the main contributor for the case group was liquor (36.4%).

Since multiplicative synergy effects between alcohol and tobacco were identified (Likelihood-ratio test $\chi^2_4 = 14.84$, $p < 0.01$), the relationship between oesophageal cancer risk and characteristics of alcohol intake was evaluated by smoking habits (Table 2). Compared to non-drinkers, current drinkers were observed to experience a 3.0 to 8.9-fold elevated risk of oesophageal cancer, with a significantly higher risk found in smokers than non-smokers (OR ratio = 3.0). While smokers who drank consistently had an elevated cancer risk at each exposure level of alcohol consumption, increased risk was simply and most obviously discovered at the highest level of alcohol exposure in non-smokers. For average daily consumption of alcohol, cancer risk discrepancy between smokers and non-smokers was linked to the intake of light (0.1–10 g/day) to moderate (10.1–30 g/day) alcohol (OR ratios = 5.5–5.7,

**Table 2 – Odds ratios (ORs) and OR ratios for oesophageal cancer associated with characteristics of alcohol consumption and tobacco smoking, Taiwan**

| Alcohol drinking / Category | Non-smokers | | Smokers | | Smoker versus Non-smoker OR ratio[a](95% CI) |
|---|---|---|---|---|---|
| | Cases/Controls | Adj. OR[a] (95% CI) | Cases/Controls | Adj. OR[a] (95% CI) | |
| Drinking habit | | | | | |
| Non-drinker | 69/531 | 1.0 (Ref) | 69/278 | 1.0 (Ref) | |
| Previous | 5/40 | 1.3 (0.5–3.7) | 146/71 | 6.9 (4.5–10.5) | 5.2 (1.7–15.6) |
| Current | 20/74 | 3.0 (1.6–5.6) | 343/133 | 8.9 (6.2–13.0) | 3.0 (1.5–6.2) |
| Age at starting drinking (years) | | | | | |
| >25 | 12/61 | 1.9 (0.9–3.9) | 139/80 | 6.6 (4.3–10.0) | 3.5 (1.5–8.3) |
| ⩽25 | 13/53 | 3.1 (1.5–6.6) | 350/124 | 9.1 (6.3–13.2) | 2.9 (1.3–6.6) |
| Years of alcohol consumption | | | | | |
| 1–20 | 8/38 | 2.1 (0.9–5.0) | 101/62 | 8.0 (4.9–13.1) | 3.9 (1.4–10.3) |
| 21–40 | 11/62 | 2.1 (0.9–4.6) | 274/102 | 9.0 (6.1–13.3) | 4.2 (1.8–10.1) |
| >40 | 6/14 | 4.0 (1.3–12.0) | 114/40 | 6.8 (4.1–11.0) | 1.7 (0.5–5.6) |
| Average alcohol intake per day (g) | | | | | |
| 0.1–10 | 3/65 | 0.6 (0.2–2.2) | 80/74 | 3.5 (2.3–5.6) | 5.5 (1.5–20.2) |
| 10.1–30 | 3/30 | 1.2 (0.3–4.1) | 116/69 | 6.6 (4.2–10.3) | 5.7 (1.5–21.9) |
| 30.1–50 | 9/11 | 9.0 (3.2–25.5) | 91/21 | 15.4 (8.5–27.7) | 1.7 (0.5–5.6) |
| >50 | 10/8 | 7.5 (2.6–22.0) | 202/40 | 16.9 (10.5–27.3) | 2.3 (0.7–7.2) |
| Frequency of alcohol intake (day/week) | | | | | |
| 1–3 | 0/67 | –[c] | 106/110 | 3.4 (2.2–5.2) | –[c] |
| 4–6 | 5/32 | 1.6 (0.6–4.6) | 108/46 | 7.7 (4.8–12.5) | 4.7 (1.5–14.9) |
| 7 | 20/15 | 10.8 (4.8–24.2) | 275/48 | 18.8 (12.1–29.1) | 1.7 (0.7–4.3) |
| Average alcohol intake per drinking day (g) | | | | | |
| 0.1–10 | 3/23 | 1.9 (0.5–6.9) | 32/25 | 4.1 (2.2–7.9) | 2.2 (0.5–9.1) |
| 10.1–30 | 3/34 | 1.0 (0.3–3.7) | 81/57 | 4.7 (2.9–7.5) | 4.5 (1.2–17.5) |
| 30.1–50 | 6/33 | 2.7 (1.0–7.2) | 132/54 | 8.7 (5.5–13.8) | 3.2 (1.1–9.2) |
| >50 | 13/24 | 5.0 (2.1–11.5) | 244/68 | 12.7 (8.3–19.4) | 2.6 (1.0–6.5) |
| Lifetime cumulative drink × years[b] | | | | | |
| 1–20 | 5/68 | 1.0 (0.4–2.7) | 97/94 | 3.9 (2.5–5.9) | 3.8 (1.3–11.1) |
| 21–40 | 3/19 | 1.8 (0.5–6.6) | 82/42 | 7.0 (4.2–11.5) | 3.9 (0.9–15.6) |
| >40 | 17/27 | 5.2 (2.4–11.0) | 310/68 | 14.2 (9.5–21.4) | 2.7 (1.2–6.4) |
| Type of alcohol beverage | | | | | |
| Beer | 15/67 | 2.7 (1.4–5.4) | 229/112 | 6.9 (4.7–10.2) | 2.6 (1.2–5.6) |
| Wine | 2/8 | 2.4 (0.4–12.9) | 48/19 | 7.9 (4.1–15.0) | 3.3 (0.5–20.0) |
| Liquor | 8/24 | 2.9 (1.1–7.5) | 131/54 | 8.3 (5.2–13.1) | 2.9 (0.9–8.5) |
| Hard liquor | 0/15 | –[c] | 81/19 | 16.5 (8.8–30.9) | –[c] |

a Odds ratios and OR ratios were derived from interaction models of drinking and smoking adjusted for study hospital, age, gender, education, pack × years of betel quid chewing and consumption of vegetables and fruits.
b One drink intake corresponds to 15.75 grams of alcohol.
c Non-appreciated.

$p < 0.05$). Given that drinkers of hard liquor had the highest cancer risk (OR = 16.5), all types of alcoholic beverages showed an association with higher risks of oesophageal cancer among smokers.

The adjusted continuous relationship between predicted log odds and average daily intake of alcohol is presented in Fig. 1. A non-linear, dose-dependent relationship was, separately, observed among non-smokers (nonparametric $\chi^2 = 13.5$, $p = 0.006$) and smokers (nonparametric $\chi^2 = 79.1$, $p < 0.0001$). In non-smokers, linearly elevated log odds were identified in alcohol consumption of about 20 to 50 g/day, whereas in smokers, a steeper linear increase in log odds was recognised below alcohol intake of 40 g/day, and more moderate afterward.

Compared with non-drinkers, the adjusted ORs for oesophageal cancer associated with average daily consumption of alcohol measured in a continuous variable are depicted in Fig. 2. With 50% of weighted window span, the findings from the GAM for light intake and, to a lesser extent, for moderate and heavy intake were compatible with those from the logistic models for the categorised variables in both non-smokers and smokers. Further, substantially heterogeneous ORs between these two groups were detected among patients who consumed light-to-moderate amounts of alcohol.

Taking the level of cumulative tobacco exposure into account, the joint effect and OR heterogeneity associated with average alcohol intake are displayed in Table 3. Among non-drinkers, patients who smoked had a 2.1 to 2.7-fold elevated risk of contracting oesophageal cancer. In contrast, among non-smokers, only patients who consumed >30 g/day of alcohol had a significant cancer risk (OR = 8.2). Compared to patients who did not have smoking and drinking habits, the joint risks within each smoking group rose as the amount of alcohol consumed increased. However, the elevated cancer risks for light-to-moderate alcohol intake were dependent on the level of tobacco exposed. Drinkers with >30 pack × years of tobacco exposure displayed a far higher heterogeneous risk than the non-smokers (OR ratio = 6.5–7.8 fold).

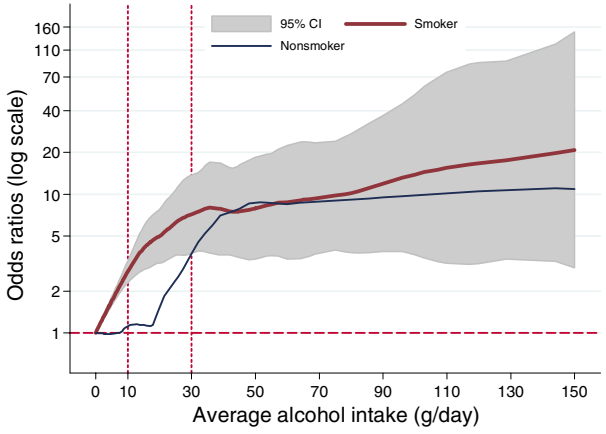


**Fig. 2 – Smoothing adjusted odds ratios, derived from generalised additive models with 50% of weighted window span, for oesophageal cancer associated with average alcohol intake (displayed in ⩽150 grams) for non-smokers and smokers, respectively.**

The frequency of alcohol intake and the quantities consumed per-drinking-day are the two constitutional components which determine the average daily consumption of alcohol. In order to distinguish the relative role of the two drinking features, as well as of the intake years and beverage types on the risk of oesophageal cancer, a two-dimensional analysis was performed among smokers (Table 4). Non-smokers were excluded because of their heterogeneous cancer risks and the limited number of subjects available to robust data analyses. Compared with non-drinkers, the oesophageal cancer risk almost always increased along with the increase of drinking frequency within strata of the three selected drinking characteristics. Adjusting additionally for the other effects of alcohol consumption, a stronger increased trend in risk was identified based on the frequency of consumption rather than for quantities consumed. Allowing for the influence of drinking frequency, no appreciable association between types of alcoholic beverage and oesophageal cancer risk was found.

The adjusted PAR% associated with smoking habits and the lowering of different levels of alcohol intake is summarised in Table 5. Among non-smokers, the consumption of light-to-moderate alcohol almost failed to explain any occurrence of oesophageal cancer (PAR% < 0.6) as reflected in their corresponding non-significant risks. In contrast, heavy alcohol consumption (⩾30 g/day) had a 17.8% of PAR%. Among smokers, alcohol intake accounted for about 76–77% of the cases of oesophageal cancer, regardless of which drinking measures were used. The highest level of alcohol exposure in both drinking quantities and frequency of consumption (partial PAR%, 46.6–49.2%) was the greatest contributor to their total PAR% (60.8–64.0% of total PAR%). Compared with the lowest exposure levels of drinking, patients who consumed heavy alcohol or drank daily still had a 4.6 to 5.5-fold significantly elevated cancer risk. Such quantities and frequency of alcohol consumption were the major contributors to their total PAR% (partial PAR%, 40.3–41.0%). Additionally, 29.0–31.6% of the etiological fraction for oesophageal cancer was attributable to the reduction of heavy to moderate alcohol intake. Due to the large proportion of beer drinkers in this population, beer consumption was associated with the greatest partial PAR% (10% in non-smokers and 34.7% in smokers) among all types of beverage.

The population impact of combined drinking habits on cancer of the oesophagus among smokers is evaluated in Fig. 3. The highest frequency of alcohol intake (7 days/week) had the greatest partial PAR% within groups of alcohol intake per drinking day. It is noteworthy that daily, heavy alcohol consumption produced a conspicuous PAR% (37.8%) for developing oesophageal carcinoma in smoking.

## 4. Discussion

This study provides convincing evidence that tobacco smoking multiplicatively modifies the carcinogenetic effect of alcohol intake on the induction of squamous cell carcinoma of the oesophagus. Findings from the logistic regression models and the generalised additive models comparatively showed

**Table 3 – Odds ratios (OR), joint effects and OR ratios for oesophageal cancer associated with average daily alcohol intake (grams) and lifetime cumulative tobacco consumption (pack × years, pys)[a], Taiwan[a]**

| Alcohol drinking /Category | Non-smokers | Smokers | | Non-smokers | Smokers | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1–30 pys | >30 pys | | 1–30 pys | 1–30 pys versus Non-smokers | >30 pys | >30 pys versus Non-smokers |
| | Cases/ Controls | Cases/ Controls | Cases/ Controls | Adj. OR[b] (95% CI) | Adj. OR[b] (95% CI) | OR ratio[b] (95% CI) | Adj. OR[b] (95% CI) | OR ratio[b] (95% CI) |
| Joint effect | | | | | | | | |
| Alcohol intake | | | | | | | | |
| No | 69/531 | 38/156 | 31/122 | 1.0 (Ref) | 2.7 (1.6–4.5) | | 2.1 (1.2–3.6) | |
| 0.1–10 | 3/65 | 35/42 | 45/32 | 0.6 (0.2–2.2) | 8.2 (4.5–15.2) | | 8.6 (4.7–15.8) | |
| 10.1–30 | 3/30 | 48/40 | 68/29 | 1.2 (0.3–4.1) | 13.1 (7.2–23.8) | | 18.6 (10.3–33.8) | |
| >30 | 19/19 | 114/29 | 179/32 | 8.2 (3.8–18.0) | 36.1 (20.2–64.6) | | 41.2 (24.0–70.7) | |
| OR heterogeneity | | | | | | | | |
| Alcohol intake | | | | | | | | |
| No | | | | 1.0 (Ref) | 1.0 (Ref) | | 1.0 (Ref) | |
| 0.1–10 | | | | 0.6 (0.2–2.2) | 3.1 (1.6–5.7) | 4.7 (1.2–18.6) | 4.2 (2.2–8.0) | 6.5 (1.6–26.0) |
| 10.1–30 | | | | 1.2 (0.3–4.1) | 4.8 (2.6–8.9) | 4.2 (1.0–17.0) | 9.1 (4.8–17.3) | 7.8 (1.9–32.4) |
| >30 | | | | 8.2 (3.8–18.0) | 13.4 (7.4–24.2) | 1.6 (0.6–4.3) | 20.1 (11.1–36.3) | 2.4 (0.9–6.5) |

a One smoking pack corresponds to 20 cigarettes.

b Odds ratios, OR ratios and joint effects were derived from interaction models of drinking and smoking adjusted for study hospital, age, gender, education, pack × years of betel quid chewing and consumption of vegetables and fruits.

**Table 4 – The joint and drinking characteristic-adjusted effects of drinking frequency and selected features of alcohol intake on oesophageal cancer among smokers, Taiwan**

| Alcohol drinking /Category | Non-drinker | Frequency of intake (days/week) | | | Intake frequency-adjusted OR[b] (95% CI) |
|---|---|---|---|---|---|
| | Cases/ Controls OR[a] | 1–3 Cases/Controls OR[a] (95% CI) | 4–6 Cases/Controls OR[a] (95% CI) | 7 Cases/Controls OR[a] (95% CI) | |
| Non-drinker | 69/278 | | | | |
| | 1.0[c] | | | | 1.0 (Ref) |
| Alcohol intake per drinking day (g) | | | | | |
| 0.1–10 | | 7/16 | 8/4 | 17/5 | |
| | | 1.2 (0.5–3.4) | 10.1 (2.7–37.3) | 11.9 (3.9–35.9) | 0.7 (0.4–1.4) |
| 10.1–30 | | 29/29 | 14/14 | 38/14 | |
| | | 3.3 (1.8–6.1) | 2.6 (1.1–6.1) | 11.2 (5.3–23.4) | 0.8 (0.4–1.3) |
| ⩾30 | | 70/65 | 86/28 | 220/29 | |
| | | 4.5 (2.8–7.3) | 11.8 (6.8–20.5) | 24.6 (14.7–41.2) | 1.7 (1.1–2.8) |
| Intake per drinking day-adjusted OR[b] | 1.0 (Ref) | 0.6 (0.3–1.3) | 1.3 (0.6–2.9) | 3.9 (1.8–8.4) | |
| Years of alcohol intake | | | | | |
| 1–20 | | 19/40 | 22/12 | 60/10 | |
| | | 2.3 (1.2–4.7) | 8.2 (3.4–19.4) | 27.4 (12.3–61.2) | 1.1 (0.6–2.0) |
| 21–40 | | 65/53 | 66/26 | 143/23 | |
| | | 4.2 (2.5–7.0) | 8.2 (4.6–14.8) | 19.9 (11.3–35.3) | 1.4 (0.8–2.2) |
| >40 | | 22/17 | 20/8 | 72/15 | |
| | | 3.1 (1.5–6.5) | 5.6 (2.2–14.4) | 11.9 (6.1–23.3) | 0.9 (0.5–1.6) |
| Drinking year-adjusted OR[b] | 1.0 (Ref) | 3.0(1.5–5.8) | 6.6 (3.3–13.2) | 19.6 (9.7–39.5) | |
| Type of alcoholic beverage | | | | | |
| Beer | | 59/60 | 54/27 | 116/25 | |
| | | 3.2 (2.0–5.3) | 6.2 (3.4–11.0) | 15.5 (8.9–27.1) | 1.1 (0.7–1.8) |
| Wine/liquor | | 38/39 | 31/16 | 110/18 | |
| | | 3.6 (2.0–6.4) | 6.4 (3.0–13.4) | 18.0 (9.8–33.1) | 1.2 (0.7–2.0) |
| Hard liquor | | 9/11 | 23/3 | 49/5 | |
| | | 3.4 (1.2–9.4) | 28.0 (7.4–105.2) | 34.2 (12.3–95.0) | 1.8 (0.9–3.4) |
| Beverage type-adjusted OR[b] | 1.0 (Ref) | 3.5 (1.9–6.4) | 7.8 (4.2–14.4) | 23.7 (12.8–44.1) | |

a Odds ratios were adjusted for study hospital, age, gender, education, pack × years of cigarette smoking and of betel quid chewing and consumption of vegetables and fruits.
b Odds ratios were additionally adjusted for the frequency, mean quantities per-drinking-day, years of intake and beverage types, where appropriate.
c Non-drinkers were the reference group in all analyses of joint effect.

that light-to-moderate alcohol drinkers who smoked have a heterogeneously greater likelihood of producing oesophageal cancer than nonsmokers. However, the cancer risk for heavy quantities of alcohol drinkers is non-discernible between nonsmokers and smokers. The frequency with which alcohol is consumed on a weekly basis exerts the strongest influence on the risk of developing this neoplasm.

Because of their combined action in the pathogenesis of oesophageal cancer, both alcohol and tobacco consumption may exert a residual confounding in the evaluation of risk associated with each other. However, our study demonstrated that, among non-drinkers, an elevated risk of oesophageal cancer is linked to all levels of tobacco consumption, and among non-smokers, to heavy amounts of alcohol intake. The findings support indications from the earlier, less powerful studies that both alcohol and tobacco can act independently of each other in the etiology of this neoplasm.[25–27] Further, in concurrence with the results from larger-scale studies,[7,13,28] our research has indicated that, independently, the risk of developing oesophageal cancer through alcohol consumption might be linked to higher levels of ethanol exposure.

Ethanol, though not its metabolites, has not been found to cause cancer in animal experiments.[4] Therefore, in contrast to tobacco, which contains many known carcinogenic chemicals,[5] its role in promoting, facilitating or enhancing malignant transformations of the oesophageal epithelium is intriguing.[27] In the present study, tobacco was found to interact with light-to-moderate amounts of alcohol in increasing the risk of oesophageal cancer in a supra-multiplicative way (OR ratio = 5.5–5.7, $p < 0.05$), whereas with heavy amounts of alcohol in a simple multiplicative model (OR ratio = 1.7–2.3, $p > 0.05$). Similar findings were observed in a cooperative study conducted in four countries of South America.[7] These results suggest that light-to-moderate alcohol consumption alone does not have a strong effect on the carcinogenesis of oesophageal epithelial cells, but perhaps as proposed by McCoy et al.,[29] acts as a solvent to increase the physical contact with tobacco-derived carcinogens, thereby facilitating the entry of the carcinogens into the oesophageal mucosa. Alternatively, acetaldehyde, a major intermediate metabolite of alcohol, is a recognised carcinogen in animal models.[30] Epidemiological studies have shown that the metabolism of acetaldehyde is more closely related to the intake of heavy

**Table 5 – Adjusted odds ratios and population attributable risk proportion (PAR%) for oesophageal cancer associated with smoking habit and the lowering of alcohol consumption Taiwan**

| Alcohol drinking / Category | Non-smokers | | | Smokers | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Controls with risk factor % | Compared with non-drinkers | | Controls with risk factor % | Compared with non-drinkers | | Compared with intake level 1 | | Compared with intake level 2 | |
| | | Adj. OR[a] (95% CI) | Adj. PAR%[a] | | Adj. OR[a] (95% CI) | Adj. PAR%[a] | Adj. OR[a] (95% CI) | Adj. PAR%[a] | Adj. OR[a] (95% CI) | Adj. PAR%[a] |
| Average alcohol intake per day (g) | | | | | | | | | | |
| Non-drinker | 82.3 | 1.0 (Ref) | | 57.7 | 1.0 (Ref) | | 0.3 (0.2–0.5) | | 0.2 (0.1–0.2) | |
| 0.1–9.9 | 10.1 | 0.6 (0.2–2.3) | 0.0 | 15.4 | 3.5 (2.2–5.4) | 10.2 | 1.0 (Ref) | | 0.5 (0.3–0.9) | |
| 10.0–29.9 | 4.7 | 1.2 (0.3–4.4) | 0.5 | 14.3 | 6.3 (4.0–9.9) | 17.5 | 1.8 (1.1–3.0) | 9.4 | 1.0 (Ref) | |
| ⩾30.0 | 3.0 | 8.5 (3.6–20.1) | 17.8 | 12.7 | 15.9 (10.3–24.4) | 49.2 | 4.6 (2.9–7.3) | 41.0 | 2.5 (1.6–3.9) | 31.6 |
| Total PAR% | | | 18.3 | | | 76.9 | | 50.4[b] | | 31.6[c] |
| Frequency of alcohol intake (day/week) | | | | | | | | | | |
| Non-drinker | 82.3 | 1.0 (Ref) | | 57.7 | 1.0 (Ref) | | 0.3 (0.2–0.5) | | 0.1 (0.1–0.2) | |
| 1–3 | 10.4 | – | –[b] | 22.8 | 3.3 (2.2–5.1) | 13.3 | 1.0 (Ref) | | 0.4 (0.3–0.7) | |
| 4–6 | 5.0 | 1.6 (0.5–4.8) | 2.0 | 9.5 | 7.5 (4.6–12.1) | 16.8 | 2.2 (1.4–3.6) | 10.7 | 1.0 (Ref) | |
| 7 | 2.3 | 11.1 (4.6–26.6) | 19.4 | 10.0 | 18.2 (11.6–28.4) | 46.6 | 5.5 (3.5–8.5) | 40.3 | 2.4 (1.5–4.0) | 29.0 |
| Total PAR% | | | 21.4 | | | 76.6 | | 51.0[b] | | 29.0[c] |
| Type of alcoholic beverage | | | | | | | | | | |
| Non-drinker | 82.3 | 1.0 (Ref) | | 57.7 | 1.0 (Ref) | | | | | |
| Beer | 10.4 | 2.7 (1.3–5.6) | 10.0 | 23.2 | 6.5 (4.4–9.6) | 34.7 | | | | |
| Wine/Liquor | 5.0 | 2.4 (0.9–6.1) | 6.2 | 15.2 | 8.0 (5.2–12.2) | 28.0 | | | | |
| Hard liquor | 2.3 | – | –[d] | 3.9 | 15.2 (8.1–28.5) | 13.6 | | | | |
| Total PAR% | | | 16.2 | | | 76.3 | | | | |

a Odds ratios were derived from logistic models for non-smokers and smokers, respectively, and were adjusted for study hospital, age, gender, education, pack × years of betel quid chewing and consumption of vegetables and fruits for non-smokers, and additional pack × years of cigarette smoking for smokers.

b Total PAR% for drinkers in alcohol level 2 and 3 reducing to level 1.

c Total PAR% for drinkers in alcohol level 3 reducing to level 2.

d Non-appreciated.

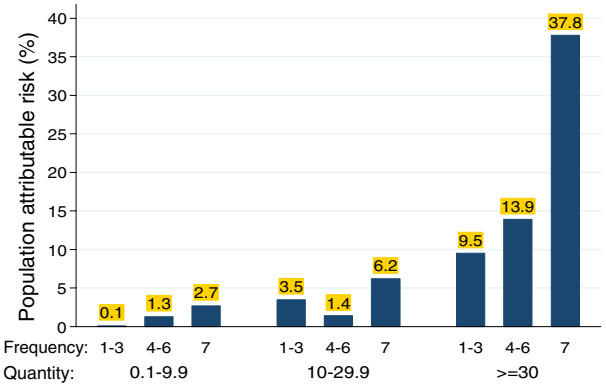


**Fig. 3 – Adjusted partial population attributable risk proportion for oesophageal cancer associated with the joint effects of drinking frequency (days/week) and quantities (grams/drinking-day) among smokers.**

alcohol, even when polymorphisms of alcohol-related metabolising genes have been taken into consideration. [31,32] Moreover, a high concentration of ethanol may directly damage oesophageal mucosa. It is, therefore, suggested that both systemic and local actions may be involved in the independent cancer risk of heavy alcohol consumption. While tobacco certainly interacts with alcohol, when compared to its effects among non-smokers, its joint chemical inter-reactions with heavy alcohol seem to simply follow a multiplicative way.

Numerous retrospective case-control investigations have detected a significantly log-linear dose-risk relationship between alcohol consumption and oesophageal cancer.[7,11,33–35] Further, our study using GAM with smoothing terms has identified a smoking habit-specific concave-shaped increase in the cancer risk curve. Such nonparametric modelling is assumption-free on the shape of the dose-dependent relationship.[20] Compared with the categorical approaches, smoothing modelling makes the assessment of the effect of alcohol on a wide range of intake possible, while the numbers of study subjects with excessive intake were restricted. On the other hand, a concave increase in the risk of suffering from oesophageal cancer implies that the risks estimated from log-linear models for a continuous variable might be underestimated in regard to the middle-range of alcohol intake, but be overestimated at low and excessive ranges of intake.

There was ample evidence in prior findings for an elevated risk of oesophageal cancer associated with heavy alcohol consumption, but there was inconsistent data supporting a higher risk associated with light-to-moderate alcohol consumption. Epidemiological reports from South India,[33] the US,[34] Northern Italy,[36] and Hong Kong[37] concordantly documented that an alcohol intake of below about 140 g/week is linked to a slight increase, or even decrease, in risk of oesophageal cancer. However, a meta-analysis found that the daily consumption of 25 grams of alcohol carried a 1.5-fold significantly elevated risk.[16] Some concerns about these risk evaluations must be noted. Statistical manipulation, achieved by simply adjusting for the main effects of tobacco smoking, as performed in many other studies, is unlikely to account precisely for the possible residual confounding that are caused by tobacco consumption. This same statistical procedure fails to account for the way in which alcohol and tobacco may multiplicatively interact with each other in raising the risk of this type of neoplasm. In the present research, the smoking-main-effect adjusted OR for the consumption of light and moderate alcohol were, separately, 2.6 and 4.8-fold (both $p < 0.05$, data not shown); but only 0.6 and 1.2-fold (both $p > 0.05$) for non-smokers, and reaching 3.5 and 6.6-fold (both $p < 0.05$) for smokers, respectively, after taking the modifying effects of tobacco usage into account. Comments by Reed[38] suggested that the summary results of the major findings should, at the very least, be provided, particularly for the nonsmoking subset of the study population.

The proper understanding of how a subject's habits of alcohol consumption influence the risk of oesophageal cancer has important implications in the prevention of the disease. Our study showed that high frequency (7 days/week) drinkers who consumed low-to-moderate levels of alcohol per-drinking-day had a higher risk of oesophageal cancer (OR = 11.2–11.9) than those of low frequency (1–3 days/week) who drank heavy quantifies of alcohol (OR = 4.5). Along the same lines, the increase in drinking characteristic-adjusted risk was evidenced to be more striking for the frequency ($p$ for trend: < 0.0001) than for the amount ($p$ for trend: 0.002) of alcohol consumed. This data clearly suggests that the carcinogenic effect of alcohol is more dependent on the frequency than the amount consumed per-drinking-day.

In this study, beer drinkers, the predominant alcohol consumers in this population, had the largest PAR% of oesophageal cancer. These findings support the hypothesis that the beverage most widely ingested by a given population is the one most likely to be associated with the development of upper digestive tract cancer in that population.[4,39] When adjusted for the effects of drinking frequency, all of the risks for the three types of beverages are weakened and reveal non-significance. A study analysing pooled data from a series of five case-control studies found that, after accounting for the effects of other important covariates, the type of beverage is not a significant predictor of oesophageal cancer risk.[7] Ethanol is the major component of alcoholic beverages that determines the risk of cancer; however, there is still no clear evidence to link specific beverages to specific cancers.[40]

Alcohol consumption is one of the modifiable lifestyle factors involved in the etiology of oesophageal cancer. Findings from this investigation demonstrated that a higher proportion of oesophageal carcinoma cases are attributed to the intake of alcohol among smokers (77%) than among all subjects (67%, data not shown). This implies that, in regard to tobacco smokers, the most obvious way to avoid oesophageal cancer is to avoid alcohol consumption. Further, the smoking subgroup of daily $\geqslant$30 grams of alcohol drinking should be regarded as the most important public health initiative target, since they exhibited the greatest partial PAR% (37.8%). On the other hand, even in the absence of smoking, alcohol consumption in this population was responsible for about 18% of cancer cases, mainly due to $\geqslant$30 g/day of intake.

Attempts have also been made to assess the results of lowered alcohol consumption and its efficacy in diminishing the occurrence of oesophageal cancer. Our data showed that 31.6% of the etiologic fraction is attributable to reducing heavy alcohol consumption to a moderate intake level. The PAR%

rose to 50.4% and 76.9% if further reducing this to light intake or to abstinence. The hazards of excessive alcohol consumption should always be emphasised. Thus, heavy drinkers should be encouraged to reduce their intake, or to discontinue the consumption of alcoholic beverages entirely.

Since, among the control participants of this research, both proportions for the users of alcohol and tobacco were compatible with those reported in two large-scale studies in Taiwan,[15,41] under-representation of drinkers and smokers in our study is improbable. In addition, a similarity in the result with respect to the major associations studied across different educational levels provided some assurance that these findings are accurate. Due to the social acceptability of alcohol and tobacco use here in Taiwan, and the openness with which study subjects have responded to our well-trained interviewers, the degree to which recall biases have arose in our study should be minimal.

In summary, the quantities of alcohol consumed in Taiwan display a direct relationship link to the smoking habit-specific, non-linear development of oesophageal cancer. High-frequency, heavy alcohol consumption substantially contributes to oesophageal cancer among the Taiwanese population. Tobacco interacts with light-to-moderate alcohol intake in a supra-multiplicative way, with heavy intake in a simple, multiplicative way.

## Conflict of interest statement

None declared.

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