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ORIGINAL ARTICLE

The association of betel quid, alcohol, and cigarettes with salivary gland tumor—A case—control study

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Received 25 November 2016; Final revision received 14 December 2016

Available online ■ ■ ■

KEYWORDS

alcohol drinking;
betel quid chewing;
cigarette smoking;
salivary gland tumor

Abstract *Background/purpose:* Salivary gland tumor (SGT) is a rare disease with a largely unknown etiology. The risks of betel quid chewing, alcohol drinking, and cigarette smoking have been well documented in oral cancer but not in SGT. We aimed to investigate the independent and combined effects of betel quid chewing, cigarette smoking, and alcohol consumption on the incidence of SGT.

Materials and methods: We conducted a case—control study of 1845 patients aged 35–65 years, including 239 patients with pathologically proven SGT and 1606 controls from the health examination clinics of the same hospital during 2005–2014 to examine the association of these three risk factors with SGT in Taiwan. Adjusted odds ratio (aOR) and their 95% confidence interval for the association of risk factors to SGT were analyzed.

Results: After adjusting for covariates, aOR of cigarette smoking, alcohol drinking, and betel quid chewing were 2.50, 1.27, and 3.38, respectively for SGT. The significantly increased risk for SGT was observed in cigarette smoking ($P < 0.001$). Cigarette smoking was also found to increase risks in subgroups of SGT (aOR = 5.24, 2.41, 2.63, and 2.04 in minor, major, benign, and malignant SGT, respectively).

Conclusion: Our study provided the first evidence to show the independent and combined impact of betel quid chewing with cigarette smoking and alcohol drinking on the SGT, and support the concept that cigarette smoking may associate with SGT carcinogenesis.

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<http://dx.doi.org/10.1016/j.jds.2016.12.002>

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Please cite this article in press as: Li T-I, et al., The association of betel quid, alcohol, and cigarettes with salivary gland tumor—A case—control study, Journal of Dental Sciences (2017), <http://dx.doi.org/10.1016/j.jds.2016.12.002>

Introduction

Neoplasms that arise in the salivary glands are relatively rare. The annual incidence of all salivary gland tumors or neoplasms ranges from 0.4 cases to 13.5 cases per 100,000 people.¹ Since the salivary gland tumor (SGT) is an uncommon neoplasm of the head and neck, there is little knowledge on its exact etiology. Risk for SGT may be increased with tobacco smoking, radiotherapy, viral infection, hair coloring and treatments, and genetic mutations; however, these have not been confirmed as risk factors.²

Environmental carcinogens, such as betel quid chewing, tobacco smoking, and alcohol drinking have been regarded as major risk factors for head and neck cancer.³ At least 75% of head and neck cancers, not including SGT, are attributable to cigarette smoking and alcohol drinking in Europe, the USA, and other developed regions.^{4,5} Furthermore, the synergistic effects of alcohol, tobacco, and betel quid on oral cavity, pharyngeal, and laryngeal cancer risk has been proposed.^{6,7} However, controversy exists over whether these factors increase the risk of SGT and the effect of betel quid chewing on salivary glands has not been explored in humans.^{8–12}

The aim of this study is to investigate the independent and combined associations of cigarette smoking, betel quid chewing, and alcohol drinking with SGT.

Materials and methods

Case and control selection

This case–control study was conducted at Tri-Service General Hospital in Taipei, Taiwan from 2005 to 2014. A total of 239 patients, aged 35 to 64 years, with a diagnosis of SGT were selected. A total of 1606 controls with the same age range were simultaneously recruited from health examination clinics. Individuals with a previous diagnosis of any other type of cancer were excluded from the study.

Collection of oral habit records and anthropometric measurements, and laboratory analysis of fasting glucose levels

Data collection included diagnoses, prescriptions, laboratory tests (including blood glucose levels measured after 12–14 hours of fasting), and oral habits (smoking status, alcohol drinking use, and betel quid chewing). Anthropometric measurements (height and weight) were recorded upon patient admission. We used a three-level indicator variable (yes/ex/no) to categorize the smokers, betel quid chewers, and alcohol drinkers. We defined habitual betel quid chewing or cigarette smoking as having at least one quid or cigarette, respectively, daily for at least 1 year, and regular alcohol drinking as drinking on more than 4 d/wk.⁶ Body mass index (BMI) was calculated by dividing weight (in kg) by squared height (in m). According to World Health Organization standards, a BMI 25–30 kg/m² was defined as overweight and a BMI of 30 kg/m² or higher was defined as obesity.¹³ A person with a fasting blood glucose \geq 126 mg/dL was considered diabetic.¹⁴

Statistical analysis

Differences in characteristics and risk factors between patients and control individuals were tested using the independent *t* test. Distributions in sex, cigarette smoking, alcohol intake, and betel quid chewing among patients and controls were evaluated using the Chi-square test. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for each possible risk factor among SGT patients using unconditional logistic regression models. To control for potential confounding effects, ORs were adjusted for other covariates. A *P* value $<$ 0.05 was used to determine statistical significance.

Results

Sociodemographic characteristics of study participants

A total of 1845 participants (239 patients and 1606 controls) with information regarding their age, sex, and sociodemographic characteristics, were included in our analyses (Table 1). According to univariate analysis, the average age and proportion of men were 50.95 ± 8.04 years and 59.4%, respectively, for SGT patients, and 50.45 ± 7.75 years and 57.6%, respectively, for controls. The incidence of habitual smoking, which included current and former smokers, was significantly higher in SGT patients (39.7%) than in controls (27.8%). In both SGT patients and controls, a history of alcohol drinking was similar (6.9% for patients and 6.4% for controls), as was a history of betel quid chewing (3.4% for patients and 3.9% for controls). SGT patients had a higher prevalence of diabetes (28.4%) than controls (5.7%). There were higher proportions of overweight and obesity in patients compared to controls (34.0% vs. 30.9% and 12.0% vs. 6.3%, respectively). Overall, the mean BMI among patients was 24.94 ± 4.05 kg/m² compared with 24.22 ± 3.55 kg/m² among controls. Significantly higher BMIs for SGT patients compared to controls were noted. Compared to the reference group, smoking, diabetes, and BMI were independent risk factors for SGT with the odds risk of 2.32, 6.50, and 2.22 (*P* $<$ 0.05) according to the univariate analysis results and 3.24, 7.43, and 1.68 (*P* $<$ 0.05) according to the multivariate analysis results, respectively.

The independent and combined effects of smoking, drinking, and chewing habits on SGT patients

The independent and synergistic effects of different combinations of habits on SGT risk are shown in Table 2. Among the 239 SGT patients, the risks associated with cigarette smoking (C), alcohol drinking (A), and betel quid chewing (B) were 2.50, 1.27, and 3.38, respectively; however, a significant increase in risk was only observed for cigarette smoking (*P* $<$ 0.001).

The risks for both betel and cigarette (B + C) users (aOR = 1.04) and for both alcohol and cigarette (A + C) users (aOR = 1.32) were calculated and compared to the risk for concomitant alcohol, betel, and cigarette (A + B + C) users (aOR = 1.29). Combined exposure of any

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