ORIGINAL ARTICLE

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

Tsung-I. Li [a], Meng-Ta Chiang [a], Kuo-Chou Chiu [a],
Ching-Huang Lai [b], Shyun-Yeu Liu [c]*, Yi-Shing Shieh [a]*

[a] Department of Dentistry, Tri-Service General Hospital, National Defense Medical Center, Taipei,
    Taiwan, ROC
[b] Department of Public Health, National Defense Medical Center, Taipei, Taiwan, ROC
[c] Department of Oral & Maxillofacial Surgery, Chi Mei Medical Center, Tainan, Taiwan, ROC

Abstract *Background/purpose:* Salivary gland tumor (SGT) is a rare disease with a largely un-known 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% confi-dence 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 sup-port the concept that cigarette smoking may associate with SGT carcinogenesis.

© 2017 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

 * Corresponding authors. School of Dentistry, National Defense Medical Center, 161, Section 6, Min-Chuan East Road, Nei-Hu, Taipei 114, Taiwan (Y.-S. Shieh); Department of Oral & Maxillofacial Surgery, Chi Mei Medical Center, 901, Zhonghua Road, Yongkang, Tainan 710, Taiwan (S.-Y. Liu).
 E-mail addresses: syliu@mail.chimei.org.tw (S.-Y. Liu), ndmcyss@mail.ndmctsgh.edu.tw (Y.-S. Shieh).

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 healtsh 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/m^2 was defined as overweight and a BMI of 30 kg/m^2 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 $\pm$ 8.04 years and 59.4%, respectively, for SGT patients, and 50.45 $\pm$ 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 $\pm$ 4.05 kg/m^2 compared with 24.22 $\pm$ 3.55 kg/m^2 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

Table 1 Description and analyses of the studied population.

	Cases, n (%)	Controls	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Age (y)	50.95 ± 8.04	50.45 ± 7.75		
Sex				
Female	97 (40.6)	681 (42.4)	1.00	1.00
Male	142 (59.4)	925 (57.6)	1.08 (0.82–1.42)	0.79 (0.40–1.16)
Smoking				
No	140 (60.3)	1094 (72.2)	1.00	1.00
Ex-smoker	12 (5.2)	152 (10.0)	0.62 (0.33–1.14)	0.71 (0.35–1.46)
Yes	80 (34.5)	270 (17.8)	2.32 (1.71–3.14)*	3.24 (2.17–4.86)*
Drinking				
No	217 (93.1)	1413 (93.6)	1.00	1.00
Ex-drinker	6 (2.6)	21 (1.4)	1.86 (0.74–4.66)	3.12 (1.00–9.78)
Yes	10 (4.3)	75 (5.0)	0.86 (0.44–1.71)	0.46 (0.20–1.06)
Betel quid chewing				
No	225 (96.6)	1448 (96.1)	1.00	1.00
Ex-chewer	5 (2.1)	54 (3.6)	0.6 (0.24–1.51)	0.27 (0.08–1.06)
Yes	3 (1.3)	5 (0.3)	3.86 (0.92–16.27)	2.54 (0.47–13.90)
Diabetes				
No	164 (71.6)	1509 (94.3)	1.00	1.00
Yes	65 (28.4)	92 (5.7)	6.5 (4.55–9.28)*	7.43 (4.96–11.13)*
BMI (kg/m^2)	24.94 ± 4.05	24.22 ± 3.55		
< 25	113 (54.0)	1004 (62.8)	1.00	1.00
25–30	71 (34.0)	493 (30.9)	1.28 (0.93–1.76)	1.18 (0.83–1.69)
≥ 30	25 (12.0)	100 (6.3)	2.22 (1.38–3.59)**	1.68 (1.17–2.90)**

Categorical variables are shown as n (%) and continuous variables as mean ± standard deviation.
BMI = body mass index; CI = confidence interval; OR = odds ratio.
*P < 0.01; **P < 0.05.
[a] With univariate analysis.
[b] With multivariate analysis.

two of the three substances did not significantly elevate risk for SGT.

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

We further analyzed the association of alcohol, betel, and cigarette use with major versus minor SGT (Table 3) and benign versus malignant SGT (Table 4). Among SGT subgroups, a significant risk from cigarette smoking was also observed in minor (aOR = 2.41), major (5.24), benign (2.63), and malignant (2.04) SGT subgroups (Tables 3 and 4). In contrast, the elevated risks associated with alcohol drinking, betel quid chewing, or any combination of these habits (A, B, and C) were not significant among SGT subgroups.

Discussion

The present study shows independent risks of alcohol drinking, cigarette smoking, and betel quid chewing in relation to SGT, and demonstrates a significant association of cigarette smoking with SGT. In agreement with our results, Horn-Ross et al[10] reported a 2-fold increase in risk in 143 men who were current smokers, as well as a significant 2.5-fold increase in risk in heavy drinkers (≥8 drinks/wk). In addition, Hayes et al[11] reported a significantly increased risk for smokers among 25 salivary gland cancer patients (9-

fold for men and 4.2-fold for women), compared to non-smokers. In another study, which included 84 salivary gland cancer patients, a significant 1.8-fold increase in risk was observed in heavy smokers.[9] In our large study with 239 SGT patients, we excluded participants younger than 35 years to avoid cancer patients more likely to have been caused by inherited gene mutations (i.e., patients associated with a

Table 2 Logistic regression model of independent and combined risk factors for cigarette smoking, alcohol drinking, and betel quid chewing for all salivary gland tumor (SGT) patients.

Cigarette smoking	Alcohol drinking	Betel quid chewing	Control, n	All SGT cases, n		
				n	aOR	95% CI
−	−	−	1058	133	1.00	1.00
+	−	−	309	77	2.50*	1.69–3.71
−	+	−	24	5	1.27	0.40–4.05
−	−	+	4	2	3.88	0.42–36.33
+	+	−	55	9	1.32	0.55–3.21
+	−	+	38	4	1.04	0.30–3.65
−	+	+	0	0	—	—
+	+	+	17	2	1.29	0.27–6.10

*P < 0.01.
aOR = odds ratios also adjusted for sex, age, body mass index, and diabetes status; CI = confidence interval.

Table 3 Logistic regression model of independent and combined risk factors for cigarette smoking, alcohol drinking, and betel quid chewing for major and minor salivary gland tumor (SGT) subgroups.

Cigarette smoking	Alcohol drinking	Betel quid chewing	Control, n	Major SGT			Minor SGT		
				n	aOR[a]	95% CI	n	aOR[a]	95% CI
−	−	−	1058	130	1.00	1.00	3	1.00	1.00
+	−	−	309	72	2.41*	1.62−3.60	5	5.24**	1.19−30.13
−	+	−	24	5	1.32	0.41−4.19	0	—	—
−	−	+	4	2	3.94	0.42−36.90	0	—	—
+	+	−	55	9	1.37	0.56−3.31	0	—	—
+	−	+	38	4	1.07	0.31−3.75	0	—	—
−	+	+	0	0	—	—	0	—	—
+	+	+	17	2	1.33	0.28−6.27	0	—	—

*P < 0.01; **P < 0.05.
aOR = adjusted odds ratios; CI = confidence interval.
 [a] Odds ratios also adjusted for sex, age, body mass index, and diabetes status.

Table 4 Logistic regression model of independent and combined risk factors for cigarette smoking, alcohol drinking, and betel quid chewing for benign and malignant salivary gland tumor (SGT) subgroups.

Cigarette smoking	Alcohol drinking	Betel quid chewing	Control, n	Benign SGT			Malignant SGT		
				n	aOR[a]	95% CI	n	aOR[a]	95% CI
−	−	−	1058	98	1.00	1.00	35	1.00	1.00
+	−	−	309	58	2.63*	1.70−4.08	19	2.04**	1.04−4.42
−	+	−	24	5	1.65	0.51−5.37	0	—	—
−	−	+	4	2	4.58	0.48−43.63	0	—	—
+	+	−	55	6	2.27	1.01−5.09	3	1.06	0.11−6.84
+	−	+	38	4	2.10	0.67−6.54	0	—	—
−	+	+	0	0	—	—	0	—	—
+	+	+	17	1	1.12	0.10−6.64	1	2.17	0.25−19.0

*P < 0.01; **P < 0.05.
aOR = adjusted odds ratio; CI = confidence interval.
 [a] Odds ratios also adjusted for sex, age, body mass index, and diabetes status.

family cancer syndrome).[15] Because certain systemic diseases and organ failure are common in the elderly population and may increase susceptibility to tumors, patients older than 65 years were also excluded.[16] Due to these study strengths, our results help clarify the relationship between oral habits and SGT risk.

We found that greater BMI is associated with increased risk of SGT. Previous studies examining the association of obesity with SGT have been controversial. In their study that included 132 salivary gland cancer patients, Pan et al[17] reported that having a BMI $\geq$ 30 kg/m^2 increased risk for SGT in men, but this association was weakened after stratification by smoking and alcohol drinking. Similarly, in a study that included 91 SGT patients, Forrest et al[18] reported that obesity, as measured by BMI, was associated with a nonsignificant increased risk of salivary gland cancers. In contrast, an earlier study by Muskat and Wynder,[19] which included 128 SGT patients reported that having a greater BMI decreased the risk of the major salivary gland cancer among men.

Our findings indicate that diabetes may be another risk factor for SGT. Several studies have reported that overweight and obesity are associated with an increased risk of diabetes.[20,21] Specifically, excessive accumulation of fatty tissue and fatty acids in portal circulation, as well as decreased hepatic glucose uptake and storage, results in insulin resistance and diabetes.[22] Epidemiological evidence supports the link between diabetes and certain cancers in different populations.[23] Obesity is strongly correlated with elevated levels of leptin, plasminogen activator inhibitor-1, and endogenous sex steroids, and decreased levels of adiponectin, resulting in insulin resistance and chronic inflammation. Proinflammatory adipokines secreted by dysfunctional adipose tissue, such as tumor necrosis factor-α and interleukin-6, are believed to be involved in carcinogenesis and cancer progression.[24] Therefore, chronic inflammation may be a possible mechanism linking obesity, diabetes, and SGT.

The effects of betel quid chewing, alcohol drinking, and cigarette smoking on oral cancer risk have been well documented, but their effect on SGT risk is unknown. In a case−control study, Ko et al[6] showed that the incidence of oral cancer was 123-fold higher in individuals who smoked, drank alcohol, and chewed betel quid, compared to abstainers. Lee et al[7] reported that concomitant (A + B + C) users had significant 96.9- and 40.3-fold higher risks for cancers of the pharynx and larynx, respectively. Combined exposure to any two of three oral habits further increased the risk for esophageal cancer by 8.8−19.7-fold and to

41.2-fold for all three substances.[25] Lee et al[7] reported that the quantity of exposure and the duration of mucosal contact of the swallowed betel quid juice are substantially less within the pharynges—laryngeal region than in the oral cavity. Thus, the independent carcinogenic effects and possible synergistic actions of cigarettes and alcohol could differ in the same manner. Major salivary glands are located far from the digestive tract and indirect contact by carcinogens might explain the lower impact of oral habits on SGT risk and the greater effect of cigarette smoking on minor SGT (OR = 5.24) compared to major SGT (OR = 2.41) observed in our study. In addition, over 90% of oral cancers originate from squamous epithelia.[26] Nonetheless, most SGTs originate from glandular epithelia encompassed by fatty tissue and fibrosis in the stroma.[27] Therefore, differences in the histopathology and structure of salivary glands and digestive tract mucosa may also explain the weakened association of SGT with oral habits.

In conclusion, our findings confirm the association of cigarette smoking with SGT risk. Moreover, this is the first report to demonstrate the relationship between betel quid and SGT, with or without the influence of smoking and alcohol. In the future, larger cohorts and benchwork research will be necessary to better understand the mechanisms by which potential risk factors, such as oral habits, obesity, and diabetes, affect SGT development.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

References

1. Ellis GL, Auclair PL, Gnepp DR. *Surgical Pathology of the Salivary Glands*, 1st ed. Philadelphia: Saunders, 1991.
2. Zarbo RJ. Salivary gland neoplasia: a review for the practicing pathologist. *Mod Pathol* 2002;15:298—323.
3. Chen YJ, Chang JTC, Liao CT, et al. Head and neck cancer in the betel quid chewing area: recent advances in molecular carcinogenesis. *Cancer Sci* 2008;99:1507—14.
4. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988;48: 3282—7.
5. Negri E, La Vecchia C, Franceschi S, Tavani A. Attributable risk for oral cancer in northern Italy. *Cancer Epidemiol BiomarK Prev* 1993;2:189—93.
6. Ko YC, Huang YL, Lee CH, Chen MJ, Lin LM, Tsai CC. Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. *J Oral Pathol Med* 1995;24: 450—3.
7. Lee KW, Kuo WR, Tsai SM, et al. Different impact from betel quid, alcohol and cigarette: risk factors for pharyngeal and laryngeal cancer. *Int J Cancer* 2005;117:831—6.
8. Spitz MR, Tilley BC, Batsakis JG, Gibeau JM, Newell GR. Risk factors for major salivary gland carcinoma. A case—comparison study. *Cancer* 1984;54:1854—9.
9. Swanson GM, Burns PB. Cancers of the salivary gland: workplace risks among women and men. *Ann Epidemiol* 1997;7:369—74.
10. Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. *Epidemiology* 1997;8:414—9.
11. Hayes RB, Bravo-Otero E, Kleinman DV, et al. Tobacco and alcohol use and oral cancer in Puerto Rico. *Cancer Causes Control* 1999;10:27—33.
12. Sadetzki S, Oberman B, Mandelzweig L, et al. Smoking and risk of parotid gland tumors: a nationwide case—control study. *Cancer* 2008;112:1974—82.
13. World Health Organization. *Report of a WHO Consultation: Obesity: Preventing and Managing the Global Epidemic.* Geneva, Switzerland: World Health Organization, 2000.
14. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2006;29:S43—8.
15. Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med* 2008;359:2143—53.
16. Boggs JG. Elderly patients with systemic disease. *Epilepsia* 2001;42:18—23.
17. Pan SY, Johnson KC, Ugnat AM, Wen SW, Mao Y, Canadian Cancer Registries Epidemiology Research Group. Association of obesity and cancer risk in Canada. *Am J Epidemiol* 2004;159:259—68.
18. Forrest J, Campbell P, Kreiger N, Sloan M. Salivary gland cancer: an exploratory analysis of dietary factors. *Nutr Cancer* 2008;60:469—73.
19. Muscat JE, Wynder EL. A case/control study of risk factors for major salivary gland cancer. *Otolaryngol Head Neck Surg* 1998; 118:195—8.
20. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol* 1997;146:214—22.
21. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. *J Epidemiol Community Health* 2000;54:596—602.
22. Nestler J, Strauss 3rd JF. Insulin as an effector of human ovarian and adrenal steroid metabolism. *Endocrinol Metab Clin North Am* 1991;20:807—23.
23. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008;300:2754—64.
24. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol BiomarK Prev* 2009;18:2569—78.
25. Lee CH, Lee JM, Wu DC, et al. 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—82.
26. Beenken SW, Urist MM. Head and neck tumors. In: Way LW, Doherty GM, eds. *Current Surgical Diagnosis and Treatment.* New York: Lange Medical Books/McGraw—Hill, 2003:282—97.
27. Syrjänen S. Age-related changes in structure of labial minor salivary glands. *Age Ageing* 1984;13:159—65.