Lifestyle Factors

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8.1 Introduction

Several factors have been previously considered as contributing to the development of OSF, including chilies, nutritional deficiency, and autoimmune disease [1]. Based on the evidence from several epidemiological studies conducted in India, Murti et al. published a review in 1995 and suggested a possible association between areca nut chewing and OSF [2]. Since then, evidence has been emerging to strengthen this causal relationship [1, 3, 4]. Areca nut is prepared and consumed in many different forms around the world. Many chewers often simultaneously use areca nut with tobacco products and/or alcohol. Therefore, it is important to consider synergistic effects, if any, that may also contribute to the risk of developing OSF.

In this chapter, we review the literature published since the year 1985 that assesses the risk of developing OSF from betel quid and areca nut with or without added tobacco; we also examine any likely synergistic effects with tobacco and/or alcohol and the dose-response effect.

8

Learning Goals

- Identify the methodological issues to assess the risk estimate of betel quid and areca nut chewing for OSF.
- Study the risk of developing OSF from betel quid and areca nut with or without added tobacco.
- Understand the synergistic effects from tobacco and/or alcohol with betel quid as well as the dose-response effect.
- Explore the association between chewing frequency and duration with severity and malignant transformation of OSF.

8.2 A Review of Methodological Issues

It is important to understand how epidemiological evidence is collected and analyzed to assess the risk estimate of a substance for a specific disorder. Several study methods could be employed, which include a cross-sectional design, case-control studies, or cohort studies. The principles underlying these different studies are outlined below.

A cross-sectional study is done in a community with a high prevalence of betel quid and areca nut chewing. A community survey is conducted by using a questionnaire to collect lifestyle information and conducting oral mucosal examinations to evaluate disease condition among participants. Odds ratio (OR) and 95% confidence intervals are often presented to show the magnitude of risk. When the OR is computed directly from cross tabulation of OSF status (usually, yes vs. no) and behavior (say, areca nut chewing vs. not chewing), it is considered as an unadjusted (or crude) OR. One may also compute ORs by using multiple (also called multivariable) logistic regression with added covariates to adjust for possible confounding effects from demographic characteristics or other lifestyle habits. This type of OR is referred to as the adjusted OR and is preferrable when tobacco smoking and alcohol drinking habits are also included in the regression analysis.

A case-control study design is used when there is relatively small number of OSF patients in the community and when there are several factors associated with chewing practices. The selection of controls is intended to balance possible demographic and associated confounding factors between cases and controls.

Cohort study is generally a common design in epidemiological studies. In this design, participants are divided into comparison groups based on their exposure status at the beginning of the study. The cohort study design is usually employed in the intervention studies of behavior changes for participants with a risk factor. In these studies, the primary outcome would be changes in chewing behaviors, and the incidence of OSF cases is usually considered as the secondary outcome. Alternatively, one may consider a retrospective cohort study based on the longitudinal data collection from participants. The rate ratios (RR, or relative risk) can be estimated by dividing the rate of new incidences in exposed group compared with the nonexposed group. In addition, when incidence rates are calculated for both exposure groups, the ratio of the two incidence rates is referred to as incidence rate ratio (IRR). In some situations, when time-to-event (disease) data are recorded, the hazard ratios (HR) or hazard rate ratios (HRR) are calculated to present the risk of chewing behavior in developing OSF.

Definition

Odds ratio (OR) is a common epidemiological measure for the association between exposure (e.g., areca nut chewing) and an outcome (e.g., OSF). The OR indicates the odds of occurring an outcome when people with exposure are compared to those without exposure. When OR is greater than 1 (OR >1 and with confidence intervals greater than one), it means that people who use areca nut would have an increased risk of OSF. When OR of any exposure is less than 1 (OR <1), the chance of occurring OSF would decrease, and the exposure is considered as a protective factor.

8.3 Epidemiological Studies Contributing to the Evidence

Epidemiological studies provide the highest level of evidence to study the risk factors associated with a specific disease. Since 1985, when IARC first evaluated the evidence on betel quid-associated disorders [5], several case-control and observational studies have been published. These reports provide updates on the knowledge of the risk of betel quid chewing in OSF from the studies conducted in the recent decades.

8.3.1 Risk from Betel Quid and Areca Nut without Added Tobacco

The potential OSF risk from chewing betel quid without added tobacco has been reported from China, India, Pakistan, Sri Lanka, and Taiwan (Table 8.1). There are five community-based studies (three observational and two case-control studies) and one hospital-based clinical study from Taiwan, and all reports support the evidence of developing OSF from chewing betel quid [6–11]. Although in Taiwan most of the betel quid chew-

Table 8.1 Epidemiologic studies for the association between betel quid and areca nut chewing with oral submucous fibrosis

Reference (publication year), study location, and period	Characteristic of cases	Characteristic of controls	Exposure categories	Odds ratio (95% confidence interval)	Study design; Reference group; adjustment for potential confounders
Betel quid and areca nut without added tobacco					
Sinor et al. (1990) [16], India	60 OSF cases confirmed in a dental clinic	60 clinic-based without oral disorders	Current chewers	78.0 (5.7–1062.5)	Design: matched case-control study Reference: occasional chewers Controls matched by age, gender, and SES Adjustment: no, 95% CIs are calculated from Table 2
Maher et al. (1994) [17], Pakistan, 1989–1990	157 OSF cases confirmed in a dental clinic	157 hospital-based without oral disorders	Pan Areca nut only	32 (6–177) 154 (34–693)	Design: matched case-control study Reference: former chewers Controls matched by age, gender, and ethnicity Adjusted by age and gender and computed by unconditional logistic regression
Yang et al. (2001) [6], Taiwan	17.6% OSF cases confirmed by dentists from a community survey of 312 participants (119 men, 193 women)	Rest of survey participants without OSF	Ever chewers	13.9 (0.8–231.0)[a]	Design: cross-sectional study Reference: never chewers Adjustment: no, calculated from Table 3
Lee et al. (2003) [7], Taiwan, 1994–1995	125 histologically confirmed OSF cases (93 men, 1 women)	876 population controls (844 men, 32 women)	Former chewers Current chewers	12.1 (2.8–51.9) 40.7 (16.0–103.7)	Design: matched case-control study Reference: never chewers Controls matched by age, gender, and area Adjusted by education and occupation in conditional logistic regression

(continued)

Table 8.1 (continued)

Reference (publication year), study location, and period	Characteristic of cases	Characteristic of controls	Exposure categories	Odds ratio (95% confidence interval)	Study design; Reference group; adjustment for potential confounders
Jacob et al. (2004) [13], India	170 OSF cases confirmed by dentists and oncologists (31 men, 139 women)	47,773 controls without oral disorders by health workers	Ever chewers among nonsmokers and nondrinkers	56.2 (21.8–144.8)	Design: case-control study Reference: never chewers Adjusted by age, gender, education, BMI in nonsmokers and nondrinkers
Ranganathan et al. (2004) [14], India, 2000–2003	185 histologically confirmed OSF cases (168 men, 17 women)	185 hospital-based controls without oral disorders	Areca nut Pan masala Betel quid	3.1 (0.8–11.7) 81.5 (5.0–1341.1) 29.0 (1.7–492.2)[a]	Design: matched case-control study Reference: no habits Controls matched by age and gender Computed by univariate logistic regression
Yang et al. (2005) [8], Taiwan	62 OSF cases patients detected by screening	62 controls without oral disorders	Only chewing habit: Both sexes Men Women	4.5 (1.2–16.9)[a] 2.9 (0.3–29.3)[a] 5.6 (1.1–28.0)[a]	Design: stratified case-control study Reference: no chewing and no smoking Stratified by age/gender groups and computed by conditional logistic regression
Chung et al. (2005) [9], Taiwan, 1998–1999	17 OSF cases detected from community survey	1075 patients examined	Only chewing habit	65.9 (3.9–999.0)	Design: cross-sectional study Reference: no chewing and no smoking Adjusted by age and smoking
Ariyawardana et al. (2006) [18], Sri Lanka	74 histologically confirmed OSF cases (61 men, 13 women)	74 hospital-based controls without oral disorders	Areca nut only Betel quid	11.8 (0.6–217.2)[a] 3.1 (0.3–30.4)	Design: matched case-control study Reference: no habits Controls matched by age and gender Adjusted by smoking and drinking and computed by unconditional logistic regression
Chen et al. (2006) [10], Taiwan, 1994–2000	23 histologically confirmed OSF cases	23 hospital-based controls without oral disorders	Betel quid	4.2 (0.5–32.7)	Design: case-control study Reference: no habits Adjusted by age, smoking, and HPV
Ahmed et al. (2006) [15], India, 2002–2004	157 histologically confirmed OSF cases	135 hospital-based controls without oral disorders	Pan Pan masala Areca nut only	41.5 (13.6–127.2) 138.2 (37.6–506.7) 172.8 (18.0–1662.5)	Design: matched case-control study Reference: never chewers Controls matched by age, gender, religion, and SES Adjustment: no, calculated from Table 7

Table 8.1 (continued)

Reference (publication year), study location, and period	Characteristic of cases	Characteristic of controls	Exposure categories	Odds ratio (95% confidence interval)	Study design; Reference group; adjustment for potential confounders
Yang et al. (2010) [11], Taiwan, 2005	89 OSF cases detected from community screening	2020 patients examined	Men		Design: cross-sectional study Reference: never chewers Adjusted by age, smoking, and drinking
			Former chewers	13.5 (3.8–46.7)	
			Current chewers	22.9 (7.3–71.7)	
			Women		
			Former chewers	9.3 (3.3–26.0)	
			Current chewers	13.0 (5.2–32.6)	
Zhang et al. (2012) [12], China	24 OSF cases detected from community screening	2356 patients examined	Former chewers Current chewers	590.3 (33.7–10329.8)[a] 202.3 (12.1–3392.4)[a]	Design: cross-sectional study Reference: never chewers Adjustment: no, calculated from Table 6
Betel quid and areca nut with added tobacco					
Sinor et al. (1990) [16], India	60 OSF cases confirmed in a dental clinic	60 clinic-based without oral disorders	Current chewers	106.4 (13.0–870.1)	Design: matched case-control study Reference: occasional areca nut chewer Controls matched by age, gender, and SES Adjustment: no, 95% CIs are calculated from Table 2
Maher et al. (1994) [17], Pakistan, 1989–1990	157 OSF cases confirmed in a dental clinic	157 hospital-based without oral disorders	Pan with tobacco	64 (15–274)	Design: matched case-control study Reference: former chewers Controls matched by age, gender, and ethnicity Adjusted by age and gender and computed by unconditional logistic regression
			With and without tobacco combined:		
			Both sexes	94 (23–394)	
			Men	136 (7–2477)	
			Women	61 (14–262)	
Hashibe et al. (2002) [19], India, 1995–1998	170 OSF cases confirmed by dentists and oncologists (31 men, 139 women)	47,773 controls without oral disorders by health workers	With and without tobacco combined:		Design: case-control study Reference: never chewers Adjusted by age, gender, education, occupation, BMI, drinking, smoking, vegetable intake, and fruit intake
			Both sexes	44.1 (22.0–88.2)	
			Men	48.6 (6.5–365.4)	
			Women	45.1 (21.5–94.8)	
Jacob et al. (2004) [13], India	170 OSF cases confirmed by dentists and oncologists (31 men, 139 women)	47773 controls without oral disorders by health workers	ever chewers among non-smokers and non-drinkers	73.0 (32.9–162.2)	Design: case-control study Reference: never chewers Adjusted by age, gender, education, BMI

(continued)

Table 8.1 (continued)

Reference (publication year), study location, and period	Characteristic of cases	Characteristic of controls	Exposure categories	Odds ratio (95% confidence interval)	Study design; Reference group; adjustment for potential confounders
Ariyawardana et al. (2006) [18], Sri Lanka	74 histologically confirmed OSF cases (61 men, 13 women)	74 hospital-based controls without oral disorders	Betel quid	16.2 (5.9–44.9)	Design: matched case-control study Reference: no habits Controls matched by age and gender Adjusted by smoking and drinking and computed by unconditional logistic regression
Ahmed et al. (2006) [15], India, 2002–2004	157 histologically confirmed OSF cases	135 hospital-based controls without oral disorders	Gutka	234.9 (74.2–743.7)	Design: matched case-control study Reference: never chewers Controls matched by age, gender, religion, and SES Adjustment: no, calculated from Table 7
Mukherjee et al. (2014) [20], India, 2012–2013	50 hospital-based OSF cases	100 hospital-based controls	Gutkha	145.4 (15.2–1397)	Design: case-control study Reference: not daily users Adjusted by sex, age, alcohol, spicy foods, employment, and education
Khan et al. (2020) [21], India, 2013–20147	73 hospital OSF cases	1007 patients with tobacco-related mucosal changes reviewed	Gutkha Betel quid	17.7 (4.9–64.6) 18.6 (5.0–69.0)	Design: cross-sectional study Reference: no smoking Adjusted by smoking habit

[a]Since the number of OSF patients without lifetime chewing habit is zero, one half is used to replace zero in the computation of odds ratio

ers are also cigarette smokers, tobacco is never added to betel quid [6]. In areca nut-only chewers, without cigarette smoking or alcohol consumption, the OR is 4.5 (95% CI, confidence interval, 1.2–16.9) in Indigenous community and 65.9 times (95% CI, 3.9–999) in Han community for developing OSF as compared to people without any risk factor [8, 9]. In addition, current users are at higher risk than former chewers (OR, 40.7 vs. 12.1 [7]; 22.9 vs. 13.5 in men and 13.0 vs. 9.3 in women [11]).

The betel quid chewing reported in Mainland China is also similar to chewers in Taiwan, in that tobacco is never added to the quid and most of the chewers are also cigarette smokers [12]. The risk of OSF in Hunan province among current chewers was 202.3 (OR, 95% CI, 12.1–3392.4) and among former chewers 590.3 (OR, 95% CI, 33.7–10,329.8). The risk for former chewers in this study is much higher than current chewers. It is possible that former chewers may stop chewing due to symptoms experienced from OSF, which is often referred to as reverse causation.

One community-based and three hospital-based case-control studies conducted in India investigated the OSF risk from betel quid and areca nut without added tobacco [13–16]. From a community-based study with 170 cases and 47,773 controls, ever chewers who were also non-smokers and nondrinkers, OSF risk was 56.2 (OR, 95% CI, 21.8–144.8) [13]. Sinor et al. [16] reported a risk of 78.0 (OR, 95% CI, 5.7–1062.5) in mawa chewers having investigated 60 OSF cases and 60 matched controls. A matched case-control study with 175 OSF cases shows a risk, among areca nut, pan masala, and betel quid users, of 3.1 (OR, 95% CI, 0.8–11.7), 81.5 (OR, 95% CI, 5.0–1341.1), and 29.0 (OR, 95% CI, 1.7–492.2), respectively [14]. The ORs in another matched case-control study were 41.5 (95% CI, 13.6–127.2) for *pan* users, 138.2 (95% CI, 37.6–506.7) for *pan masala* users, and 172.8 (95% CI, 18.0–1662.5) for users of areca nut only [15]. A similar risk pattern was seen in a matched case-control study from Pakistan [17], with the reported OR for *pan* users being 32 (95% CI, 6–177) and 154 (95% CI, 34–693) for users of areca nut only.

In Sri Lanka, OR of OSF is 3.1 (95% CI, 0.3–30.4) for betel quid users and 11.8 (95% CI, 0.6–217.2) for users of areca nut only [18]. Three studies have ORs for areca nut-only users [14, 15, 18], and only one had significant OR (172.8, 95% CI, 18.0–1662.5 [15]). Users of betel quid without tobacco are reported to have a significant risk of developing OSF.

8.3.2 Risk from Betel Quid and Areca Nut with Added Tobacco

Risk from betel quid and areca nut with added tobacco has been reported from India, Pakistan, and Sri Lanka (Table 8.1). There are four hospital-based case-control studies and one community-based case-control study from India that reported risk factors for OSF [13, 15, 16, 19–21]. In the community-based study, areca nut chewers with and without added tobacco have an OSF risk of 44.1 (OR, 95% CI, 22.0–88.2) [19]. Another report from the same study center indicated an OR of 73.0 (95% CI, 32.9–162.2) for ever chewers who were also nonsmokers and nondrinkers [13]. For *gutkha* (which contains both areca nut and tobacco), the OR ranges from 17.7 (95% CI, 4.9–64.6) [21] to 234.9 (95% CI, 74.2–743.7) [15].

The risk of betel quid with added tobacco is 16.2 (OR, 95% CI, 5.9–44.9) reported from Sri Lanka [18] and 18.6 (OR, 95% CI, 5.0–69.0) from India [21].

There are three publications [13, 15, 18], which investigated ORs from both types of quid. To examine whether betel quid with tobacco added has higher risk for OSF than betel quid without tobacco, random effect pooled OR estimates were calculated by the Review Manager 5.4.1 using inverse variance method as shown in Fig. 8.1. The pooled OR estimate from Taiwan is 14.2 (95% CI, 4.1–48.8). The pooled OR estimates from

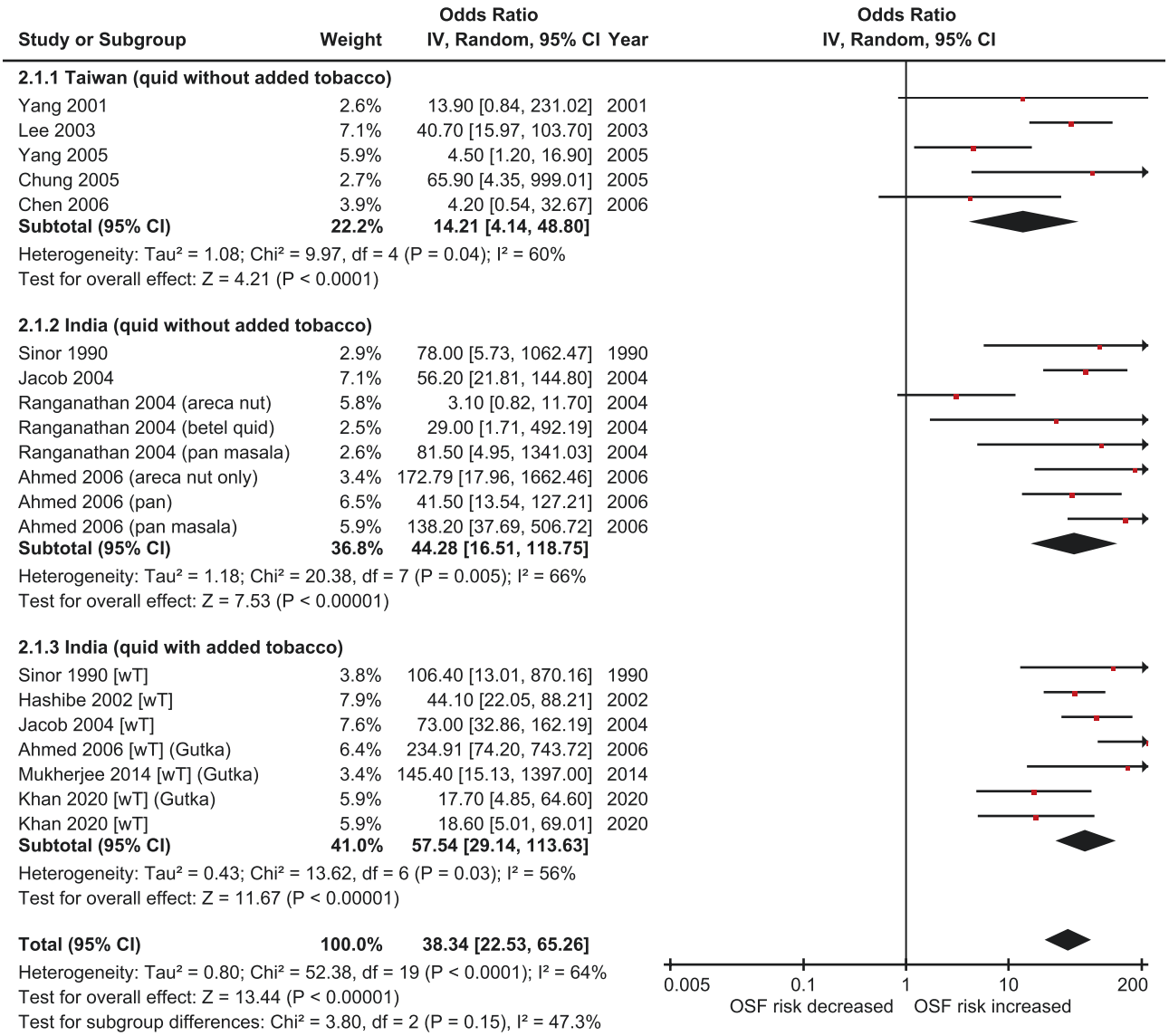

Fig. 8.1 Pooled estimates for studies from India and Taiwan

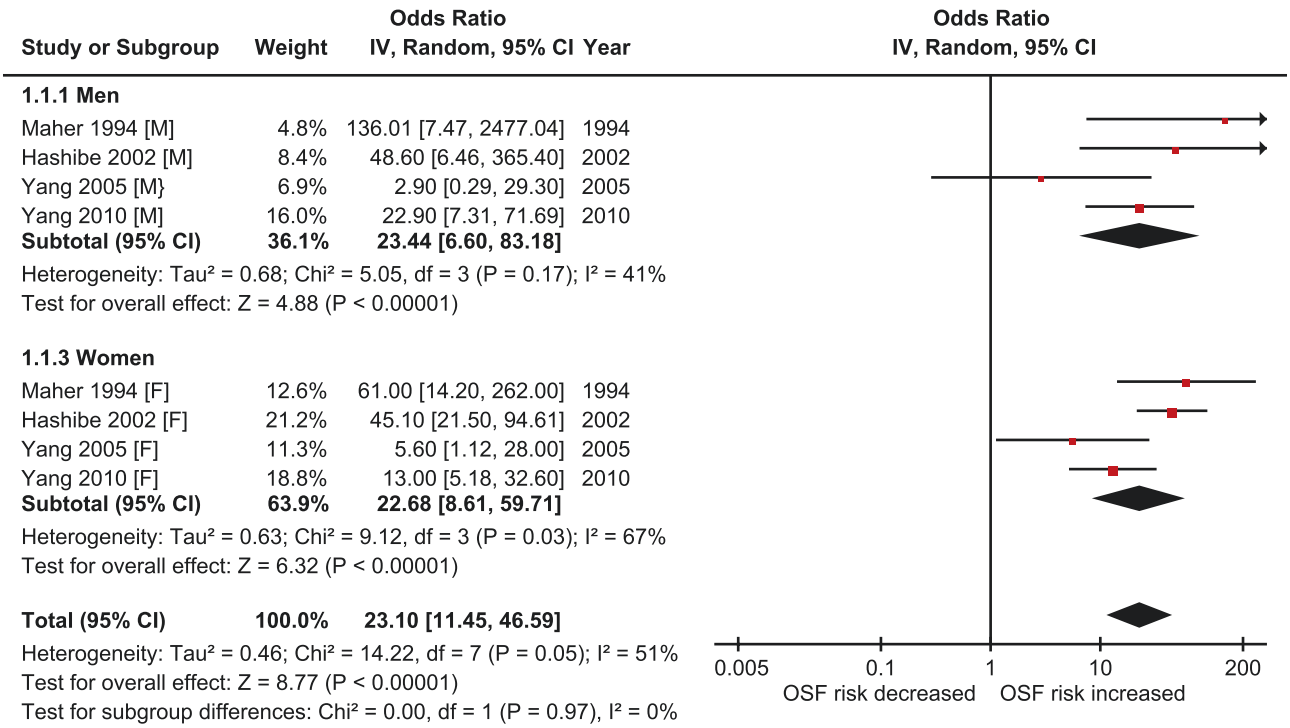

Fig. 8.2 Pooled estimates for men and women comparison

India are 44.3 (95% CI, 16.5–118.8) for nontobacco-added quid and 57.5 (95% CI, 29.1–113.6) for tobacco-added quid. The risks estimated from ORs are higher in betel quid with tobacco than quid without tobacco.

The OSF risk between men and women was also evaluated by random-effect pooled estimates. As shown in Fig. 8.2, the pooled OR was slightly higher in men (23.4; 95% CI, 6.6–83.2) than in women (22.7; 95% CI, 8.6–59.7).

8.4 Tobacco, Alcohol, and Synergistic Effect

Users of betel quid and areca nut often simultaneously engage in tobacco smoking or alcohol drinking. The synergistic effects from smoking or drinking alcohol are summarized in Table 8.2. Several studies have investigated the association between tobacco (six reports, [7, 9, 11, 18, 21, 22]) or alcohol (three reports, [7, 18, 21]) and OSF (Table 8.2). The OSF risk in chewers with smoking tobacco ranges from 0.7 (OR, 95% CI, 0.2–3.0) to 29.7 (OR, 95% CI, 3.4–259.9). Among the six studies, only two [7, 9] reported significant ORs for the association between smoking and OSF. The OSF risk in chewers who drank alcohol ranges from 0.9 (OR, 95% CI, 0.2–4.3) to 2.1 (OR, 95% CI, 1.0–4.4). Two studies from Taiwan investigated the synergistic index for the risk of OSF from smoking and alcohol drinking in addition to chewing habit [7, 9]. The synergistic index ranges from 1.2 to 1.6 and was not significant.

There is no strong association between only smoking or alcohol drinking with OSF. This is consistent with the fact that betel quid and areca nut chewing is the etiological factor for OSF.

Table 8.2 Epidemiologic studies for the association between smoking/drinking and synergistic effects and oral submucous fibrosis

Reference (publication year), study location, and period	Exposure categories	Odds ratio (95% Confidence Interval)	Synergistic categories	Synergistic index (95% confidence interval)
Maher et al. (1994) [17], Pakistan, 1989–1990			Population attributable risk, PAR	98.6%
Lee et al. (2003) [7], Taiwan, 1994–1995	Smoking		Synergistic index:	
	Past	6.5 (1.9–22.3)	Cigarette smoking	1.4 (0.4–4.7)
	Current	7.0 (3.5–14.3)	Alcohol drinking	1.2 (0.6–2.5)
	Drinking		Population-attributable risk, PAR	84.5%
	Past	1.4 (0.6–3.4)		
	Current	1.8 (1.1–3.1)		
Chung et al. (2005) [9], Taiwan, 1998–1999	Smoking only	29.7 (3.4–259.9)	Synergistic index	1.6
Ariyawardana et al. (2006) [18], Sri Lanka	Smoking	2.8 (0.5–14.1)		
	Alcohol	0.9 (0.2–4.3)		
Amarasinghe et al. (2010) [22], Sri Lanka, 2006–2007	Daily smoker	0.7 (0.2–3.0)		
	Ever smoker	1.2 (0.3–5.2)		
Yang et al. (2010) [11], Taiwan, 2005	Smoking			
	Men			
	Former	5.6 (1.6–19.6)		
	Current	2.2 (0.9–5.3)		
	Women			
	Current	1.1 (0.3–3.3)		
	Drinking			
	Men			
	Current	0.7 (0.3–1.6)		
	Women			
	Current	1.0 (0.5–1.8)		
Khan et al. (2020) [21], India, 2013–2014	Smoking	0.7 (0.4–1.3)		
	Drinking	2.1 (1.0–4.4)		

8.5 Dose-Response Effect of Betel Quid and Areca Nut

The dose-response effects from daily frequency and duration of chewing in years are reported in ten studies [7, 8, 11, 13, 16, 17, 19, 20, 23, 24] (Table 8.3). Increase in daily chewing frequency is associated with increased OSF risk. Majority of these dose-response estimates have strictly increasing trend. Studies that included tests for increasing trend do reveal significant trend effect. In terms of duration of chewing years, four studies report that OR estimates with increasing trend were only seen in women in one study [11]. A reverse trend was observed from two studies [13, 19].

In the investigation of dose-response effects, prespecified intervals of 5 or 10 are commonly used in the literature. Yang et al. [11] used the receiver operating characteristic (ROC) curve with the area under the ROC curve (AUC) to compare the diagnostic accuracy between daily chewing frequency and duration and to

Table 8.3 Epidemiologic studies for the dose-response relationship of betel quid and areca nut chewing with oral submucous fibrosis

Reference (publication year), study location, and period	Exposure categories	Odds ratio (95% confidence interval)	*p*-value for trend
Sinor et al. (1990) [16], India	Frequency		Note: ORs are calculated from Tables 2 and 3
	Times/day		
	1–5	62.4 (7.4–528.5)	
	6–15	144.3 (17.6–1183.4)	
	16+	234.0 (12.8–4261.3)	
	Duration		
	Years		
	1–5	66.3 (7.9–559.6)	
	6–10	124.8 (13.5–1154.2)	
	11+	169.0 (19.2–1486.7)	
Maher et al. (1994) [17], Pakistan, 1989–1990	Frequency		
	Times/day		
	1–5	84 (20–360)	
	6–10	246 (47–1278)	
	11+	100 (19–522)	
	Duration		
	Years		
	1–5	72 (17–316)	
	6–10	137 (29–640)	
	11+	109 (25–479)	
Hashibe et al. (2002) [19], India, 1995–1998	Frequency		
	Times/day		
	1–20	28.9 (16.5–50.5)	<0.0001
	21–40	46.8 (24.3–90.2)	
	41+	84.3 (32.8–216.8)	
	Duration		
	Years		

Table 8.3 (continued)

Reference (publication year), study location, and period	Exposure categories	Odds ratio (95% confidence interval)	*p*-value for trend
	1–20	30.8 (17.6–53.8)	<0.0001
	21–40	34.7 (18.6–64.5)	
	41+	22.7 (9.0–57.5)	
Lee et al. (2003) [7], Taiwan, 1994–1995	Frequency		
	Pieces/day		
	1–10	31.4 (11.9–82.5)	<0.05
	11–20	37.4 (12.6–110.4)	
	21+	53.5 (16.4–174.8)	
	Years		
	1–10	30.9 (11.3–84.7)	<0.05
	11–20	41.9 (14.1–124.9)	
	21+	39.3(11.7–131.7)	
	Cumulative pack–years		
	1–10	26.5 (10.0–70.3)	<0.05
	11–20	47.0 (15.8–139.8)	
	21+	51.4 (16.5–159.7)	
Jacob et al. (2004) [13], India	Frequency		
	Times/day		
	1–10	24.6 (9.4–64.3)	<0.0001
	11+	130.9 (35.6–481.5)	
	Duration		
	Years		
	1–10	34.4 (13.5–88.1)	<0.0001
	11+	17.6 (4.18–74.3)	
Yang et al. (2005) [8], Taiwan	Counts/day		
	1–9	3.7 (0.7–18.9)	
	10–29	4.6 (1.2–17.8)	
	30+	10.3 (2.4–44.7)	
Yen et al. (2007), Taiwan, 1998–1999	Frequency		
	Pieces/day		
	1–10	1.3 (0.9–1.7)	
	11–20	3.9 (2.8–5.6)	
	21+	6.9 (5.0–9.6)	

(continued)

Table 8.3 (continued)

Reference (publication year), study location, and period	Exposure categories	Odds ratio (95% confidence interval)	*p*-value for trend
Yang et al. (2010) [11], Taiwan, 2005	Men		
	Counts/day		
	1–10	25.6 (5.5–118.3)	<0.0001
	11–20	27.5 (5.3–144.1)	
	20+	33.5 (7.8–143.0)	
	Years		
	0–10	42.6 (8.7–207.9)	<0.0001
	11–20	5.0 (0.7–33.2)	
	20+	25.5(7.7–84.1)	
	Count–years		
	1st tertile	40.5 (7.5–218.1)	0.0114
	2nd	37.7 (7.6–187.4)	
	3rd	22.3 (4.0–123.2)	
	Women		
	Counts/day		
	1–10	6.5(1.9–22.9)	0.0029
	11–20	18.9 (5.6–63.9)	
	20+	17.5 (5.6–55.2)	
	Years		
	0–10	7.3 (2.0–25.8)	<0.0001
	11–20	8.2 (2.2–30.0)	
	20+	13.9 (4.7–40.5)	
	Count–years		
	1st tertile	5.2 (1.2–23.4)	0.0143
	2nd	19.2 (5.0–73.5)	
	3rd	16.1 (4.1–63.3)	
Mehrotra et al. (2013) [24], India, 2006–2009	Dose/day		
	Betel quid		
	1–2	0.8 (0.3–1.8)	
	3+	2.6 (1.1–6.4)	
	Pan masala		
	1–2	14.1 (7.5–26.5)	
	3+	17.7 (9.2–34.1)	
Mukherjee et al. (2014) [20], India, 2012–2013	Gutkha		
	2 packs/day	3.9 (0.9–18.4)	
	3–4 packs/day	11.8 (3.5–39.5)	
	5+ packs/day	89.0 (22.5–352.0)	

identify the cutoff points in dose-response measures. They found that daily chewing frequency is a better dose-response measure than duration of chewing for predicting the risk of OSF. The cutoff points for higher risk were as low as five for women (sensitivity = 79%, specificity = 83%) and two for men (sensitivity = 82%, specificity = 87%).

8.6 Dose-Response of Betel Quid and Areca Nut in Increasing Severity of OSF and Malignant Transformation

The clinical severity of OSF is also associated with the frequency and duration of using betel quid and areca nut. A cross-sectional study of 390 patients with mild (50.5%), moderate (28.2%), or severe (21.3%) OSF [25] found that the severity of OSF increased with frequency, duration, as well as time taken for chewing a quid. Patients who kept the quid in the mouth for longer periods and swallowed the betel juice had a higher risk of severe OSF.

Another cross-sectional study of 765 patients examined the areca nut dose-response effect [26]. The multinomial logistic regression, which simultaneously estimates OR for severe vs. mild and moderate vs. mild, showed that daily frequency is associated with severity (ORs = 1.13 and 1.56, all p-value <0.001). However, from the same analysis model, the effect of chewing years was not significantly associated with OSF severity. The cumulative amount of *gutkha* consumption was also found to be positively related to the clinical severity of OSF [27]. A study of 300 OSF patients showed a positive association with the duration of *gutkha* intake but not the daily frequency [28]. Another study of 342 OSF patients also showed positive association between duration and OSF severity [29]. A study of 1000 OSF cases from Central India found that both average daily frequency (1.2 vs. 0.3, p-value = 0.001) and chewing years (2.4 vs. 0.74, p-value = 0.006) were significant for malignant transformation [30].

A case-control study from China investigated the risk of malignant transformation in OSF patients [31]. The ORs increased as frequency and duration increased for chewing areca nut (alone or with smoking and alcohol drinking).

8.7 Conclusions

The consumption of betel quid and areca nut is the primary cause of OSF. Published studies reviewed in this chapter present sufficient evidence to support this conclusion. Although areca nut may be used in various forms around the world, the OSF risk posed by areca nut has been consistently confirmed from epidemiological studies in users of betel quid and areca nut with and without added tobacco. To avoid possible confounding factors, which may jeopardize the actual association, many of the studies are based on case-control design with or without matching. Matching based on age and sex would balance the possible difference from general demographic characteristics. Some studies additionally consider social economic status for matching to account for possible social or cultural differences. In several published studies, the possible confounding effects from tobacco or alcohol consumption have been addressed by multivariate logistic regression with adjustment for tobacco and alcohol use or by stratified groups.

From studies reporting dose-response by examining the daily frequency and duration of use, the effect is clearer for daily frequency, but not duration.

The association between tobacco or alcohol habits with OSF is not conclusive and furthermore does not demonstrate any synergistic effect.

Betel quid and areca nut chewing are the primary lifestyle factors increasing the risk of OSF in humans.

Summary

- We conclude that betel quid and areca nut chewing are the primary lifestyle factors for the causation of OSF.
- Daily frequency is the better dose-response measure for predicting the risk of OSF. The cutoff points for higher risk are as low as five times per day for women and two for men.
- Analyzing the current literature, there is no strong association between smoking or alcohol drinking and OSF.

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