

## RESEARCH ARTICLE

# Tobacco (*Kretek*) Smoking, Betel Quid Chewing and Risk of Oral Cancer in a Selected Jakarta Population

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### Abstract

**Purpose:** This study aimed to determine the association between tobacco consumption (*kretek*) and betel quid chewing with oral cancer risk. **Materials and Methods:** A total of 81 cases of oral cancers were matched with 162 controls in this hospital-based study. Information on sociodemographic characteristics and details of risk habits (duration, frequency and type of tobacco consumption and betel quid chewing) were collected. Association between smoking and betel quid chewing with oral cancer were analysed using conditional logistic regression. **Results:** Slightly more than half of the cases (55.6%) were smokers where 88.9% of them smoked *kretek*. After adjusting for confounders, smokers have two fold increased risk, while the risk for *kretek* consumers and those smoking for more than 10 years was increased to almost three-fold. Prevalence of betel quid chewing among cases and controls was low (7.4% and 1.9% respectively). Chewing of at least one quid per day, and quid combination of betel leaf, areca nut, lime and tobacco conferred a 5-6 fold increased risk. **Conclusions:** Smoking is positively associated with oral cancer risk. A similar direct association was also seen among betel quid chewers.

**Keywords:** Mouth neoplasms - oral cancer - Indonesia - tobacco - *Kretek* - betel quid

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### Introduction

Oral cancer incidence trend worldwide showed striking geographic and ethnic variations, which is largely attributable to the practice of risk factors. It is more prevalent in Asian as compared to Western countries, and this is could be attributed to distinct cultural practices such as varying types and patterns of tobacco use (smoked and/or chewed) and the habit of betel quid chewing among Asians (Krishna et al., 2012).

Tobacco use has been recognized as a strong risk factor for cancer where it is classified as a Group 1 carcinogen (IARC, 1986). Since a pioneer study by Wynder & Bross (1957), the role of tobacco consumption in oral carcinogenesis has been consistently demonstrated by numerous studies, including huge cohort studies (Znaor et al., 2003; Muwonge et al., 2008; Rosenquist, 2008; Javalekshmi et al., 2011; Madani et al., 2012). Moreover, findings from a nationally representative sample in India which have among the highest prevalence of oral cancer in the world showed that tobacco-related cancers accounted for 42% and 18.3% of male and female deaths respectively, where there were twice as many deaths among oral cancer

as compared to lung cancer (Dikshit et al., 2012). A recent study noted that the prevalence of oral potentially malignant lesions among smokers is 10.5% (Al-Attas et al., 2014), while 61.8% of patients who smoked tobacco were found to have clinically detectable oral mucosa changes (Sujatha et al., 2012). A dose-response relationship was also evident where smoking for a longer duration and frequency were found to confer an increased risk for malignant lesions (Loyha et al., 2012).

Indonesia is the fifth largest tobacco-consuming country in the world with an estimated consumption of 215 billion cigarettes per year (Tiandra, 2006). In 2004, the Indonesian National Health Survey reported the prevalence of smoking at 65.2% for males and 4.5% for females, but even more alarming is the finding that the prevalence among adolescents is as high as 24.5% among boys and 2.3% among girls where 30.9% of them reported smoking their first cigarette before the age of ten (Aditama et al., 2008). *Kretek* is an aromatic cigarette originating from Indonesia and is only smoked in this population. *Kretek*, which typically contains tobacco (approximately 60-85%), chopped clove buds (15-40%) and a brand-specific flavouring 'sauce' (Hanusz, 2000) is

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the preferred tobacco product, accounting for about 90% of the cigarettes consumed among Indonesians (MOHRI, 2004).

Apart from being smoked, tobacco is also chewed in the form of betel quid in some populations. It is a widely practiced risk habit in Asian countries such as Pakistan, India, Sri Lanka, Bangladesh, and Taiwan where numerous studies have reported a dose-response relationship of increased oral cancer risk with the practice of this habit (Balaram et al., 2002; Muwonge et al., 2008; Amarasinghe et al., 2010; Lin, 2011; Loyha et al., 2012). A recent study among tobacco users found that tobacco chewers had a 13-fold increased risk for development of oral lesions (Al-Attas et al., 2014). Although variations can be seen in the content of a betel quid across the different countries, a typical quid would contain areca nut, slaked lime and flavouring ingredients which are wrapped in betel leaf. In some populations, tobacco is also added to the quid. A recent study by the Asian Betel Quid Consortium of South and East Asia found that Nepal had the highest prevalence of betel quid chewing (with tobacco), with Indonesia being the second highest, while all chewers from Taiwan and Mainland China chewed betel quid without tobacco (Lee et al., 2011). In Indonesia, betel quid chewing is practiced for the most part in rural areas and it is historically practiced by elderly females as a way of showing appreciation when guests come visiting, or during festivities such as weddings and cultural events. The adverse effects of betel quid chewing is duly recognized where in 2003, betel quid alone (without tobacco) is declared as a human carcinogen (IARC, 2004).

Although consumption of tobacco, either in the form of cigarettes or chewed as part of a betel quid has been recognized as important risk factors for oral cancer worldwide, data on the Indonesian population is not available. In view of Indonesia being among the top five consumers of tobacco in the world, coupled with the fact that there is no national data on the incidence of oral cancer, information on the association between tobacco use and oral cancer is of paramount importance as such findings could provide data on the magnitude of this disease in this population, thus facilitating efforts on formulation of related policies and cessation programs. Therefore, this study was undertaken to determine the association between tobacco (*kretek*) smoking and betel quid chewing with oral cancer risk.

## Materials and Methods

### Study population

A hospital based, case-control study was conducted in five major referral hospitals in Jakarta, the capital city of Indonesia from January 2005 until April 2006. Cases were individuals with histologically confirmed oral squamous cell carcinoma who sought treatment in the selected centers. Non-Indonesian citizens and those who had previous history of cancer, cardiovascular disease or are currently undergoing treatment were excluded from this study.

Eighty one eligible cases aged 23-74 years (mean age 47.4 years $\pm$ 12.4) were recruited, while one hundred and

sixty two hospital-based controls matched for age and sex ( $\pm$ 5 years) were selected for this study (Case to control ratio of 1:2). Controls were selected among non-cancer patients who attended the same centers for minor ailments.

### Data collection

A structured questionnaire developed for the Indonesian population was used to collect data via face-to-face interview for both cases and controls. Information on sociodemographic characteristics and risk habits (tobacco smoking and betel quid chewing) was collected where details of the practice of risk habit such as duration, frequency and type were documented. For identification of type of tobacco consumed, respondents were asked to only indicate the type of tobacco that they mostly consume over the last 10 years/consumed the longest. This questionnaire was validated and pre-tested prior to its use in the field. Informed consent was obtained from all participants prior to data collection, and medical ethics approval for this study was obtained from Trisakti University, Indonesia and University of Malaya, Kuala Lumpur, Malaysia.

### Statistical analysis

The association between smoking and betel quid chewing with oral cancer risk was analysed using conditional logistic regression. Univariate logistic regression was carried out to obtain the crude odds ratio (OR). Multivariate logistic regression was then performed for variables which have  $p > 0.250$  in the univariate model (Schlesselman, 1982). A variable was considered to be a confounder if its inclusion in a model changed the OR estimation by more than 10%. The variables that fulfill these criteria as confounders are kept in the models presented with OR estimated by method of maximum likelihood. The 95% confidence intervals (95% CI) were based on the standard error of coefficient estimated and  $p$  value was obtained. All statistical analysis was carried out using SPSS version 12 and STATA version 8.

**Table 1. Sociodemographic Characteristics of Study Population**

		Case n (%)	Control n (%)	Totaln (%)
Gender	Male	50 (61.7)	100 (61.7)	150 (61.7)
	Female	31 (38.3)	62 (38.3)	93 (38.3)
Age(Mean $\pm$ SD= 47.04 $\pm$ 11.97)				
	20-34	16 (19.8)	24 (14.8)	40 (16.5)
	35-49	30 (37.0)	69 (42.6)	99 (40.7)
	$\geq$ 50	35 (43.2)	69 (42.6)	104 (42.8)
Ethnicity	Malay	71 (87.7)	134 (82.7)	205 (84.4)
	Eastern Indonesia	7 (8.6)	10 (6.2)	17 (7.0)
	Chinese origin	3 (3.7)	18 (11.1)	21 (8.6)
Diet pattern				
	Non vegetarian	78 (96.3)	149 (92.0)	227 (93.4)
	Vegetarian	3 (3.7)	13 (8.0)	16 (6.6)
Family history of cancer				
	No	68 (84.0)	139 (85.8)	207 (85.2)
	Yes	13 (16.0)	23 (14.2)	36 (14.8)
Smoking status				
	Non-smoker	36 (44.4)	83 (51.2)	119 (49.0)
	Smoker	45 (55.6)	79 (48.8)	124 (51.0)
Betel quid chewing status				
	Non-chewer	75 (92.6)	159 (98.1)	234 (96.3)
	Chewer	6 (7.4)	3 (1.9)	9 (3.7)

## Results

Males make up about two-third of the study population, with the majority of them aged 50 years old and above. A large proportion was of Malay ethnicity (93.4%) and only 6.6% were vegetarian. Among the cases, the most common sub-site was tongue (59.3%), followed by gingiva (19.8%) and buccal mucosa (11.1%) (Table 1).

Table 2 shows the distribution of smoking and betel quid chewing habit in terms of duration, frequency and type of tobacco/quid. Most of the cases were found to be smokers (55.6%) while the majority of the controls were non-smokers (51.2%). In this population, *kretek* is the preferred tobacco product with 88.9% consumers among the cases and 67.1% among controls and the majority of both cases and controls had smoked more than 10 years. A larger proportion of cases were found to be smoking higher number of sticks per day as compared to controls and conversely, more cases were found to be heavy smokers (according to Brickman Index) as compared to controls. Although prevalence of betel quid chewing is very low, a larger proportion of chewers were seen among cases (7.4%) as compared to controls (1.9%). All of the chewers included tobacco in their quid and almost all of them chewed less than 5 quid per day.

The oral cancer risk for smoking habits is shown in Table 3. Univariate analysis showed that the risk of developing oral cancer was higher among smokers compared to non-smokers (OR 1.58, 95%CI 0.81-3.09) and there is an evident trend of increasing risk with increasing number of sticks smoked per day. However, these findings were not statistically significant. In terms of type of tobacco product consumed, those who smoked *kretek* were found to have double the risk of oral cancer compared to cigarettes smokers (OR 1.91, 95%CI 0.98-3.95). Significant findings were noted in the category of user where moderate and heavy smokers were found to have 2 and 4 times increased risk of oral cancer (OR 2.31 95%CI 1.24-10.78, OR 4.38 95%CI 1.09-17.63).

Almost all variables studied (smoking status, duration of years, type of tobacco, and user category) showed

significant findings in the multivariate model, after adjusting for alcohol consumption, betel quid chewing and dietary pattern (Table 3). Smokers were found to have two times increased risk (OR 2.09 95%CI 1.01-4.32), while the risk for those who smoke for more than 10 years and those who smoked *kretek* is increased almost three-fold. Similarly, a significant four times increased risk was found for those categorized as moderate and heavy smokers.

Table 4 shows the oral cancer risk for betel quid chewing. Univariate analysis found that the practice of betel quid chewing, chewing of least one quid per day, and quid combination of betel leaf, areca nut, lime and tobacco were significantly associated with increased risk of oral cancer. These associations were found to remain statistically significant, and even slightly stronger after allowing for confounders in the multivariate model (OR

**Table 2. Smoking and Betel Quid Chewing Habit of Study Population**

		Case n (%)	Control n (%)
Smoking status	Non-smoker	36 (44.4)	83 (51.2)
	Smoker	45 (55.6)	79 (48.8)
Type of tobacco	Cigarette	5 (11.1)	26 (32.9)
	<i>Kretek</i>	40 (88.9)	53 (67.1)
Duration (years)	1-5	4 (8.9)	12 (15.2)
	6-10	4 (8.9)	18 (22.8)
	>10	37 (82.2)	49 (62.0)
No of sticks/day	1-10	19 (42.2)	48 (60.8)
	11-20	21 (46.7)	25 (31.6)
	>20	5 (11.1)	6 (7.6)
Brickman Index	1-299 (Light)	25 (55.6)	61 (77.1)
	300-599 (Moderate)	14 (31.1)	14 (17.8)
	>599 (Heavy)	6 (13.3)	4 (5.1)
Betel quid chewing status			
Non-chewer		75 (92.6)	159 (98.1)
Chewer		6 (7.4)	3 (1.9)
Type of betel quid	Betel leaf+areca nut+lime+tobacco	6 (100.0)	3 (100.0)
	Others	0 (0.0)	0 (0.0)
	Duration (years)		
1-5		0 (0.0)*	0 (0.0)
6-10		0 (0.0)	2 (66.7)
>10		4 (100.0)	1 (33.3)
No of quid/day	1-4	4 (80.0)*	3 (100.0)
	≥5	1 (20.0)	0 (0.0)

\*numbers do not add up due to missing data

**Table 3. Univariate and Multivariate Analysis of Smoking Habits and Risk for Oral Cancer**

Variables	Crude OR	95% CI	p	Adjusted OR <sup>a</sup>	95% CI	p	
Smoking status	Non-smoker	1	†	1	†		
	Smoker	1.58	0.81-3.09	0.181	2.09	1.01-4.32	0.049
No of sticks/day	None	1	†	1	†		
	1-10	1.16	0.54-2.48	0.711	1.58	0.70-3.58	0.275
	11-20	2.22	1.00-4.93	0.051	2.78	1.16-6.65	0.022
	21-50	2.35	0.60-9.20	0.221	3.1	0.74-13.02	0.123
Duration of years	None	1	†	1	†		
	1-5	0.77	0.23-2.54	0.666	0.78	0.19-3.21	0.735
	6-10	0.68	0.19-2.41	0.548	0.77	0.20-3.00	0.712
	10-55	2.25	1.06-4.78	0.034	2.98	1.30-6.83	0.01
Type of tobacco	None	1	†	1	†		
	Cigarettes	0.52	0.17-1.62	0.26	0.69	0.21-2.25	0.543
	<i>Kretek</i>	1.91	0.98-3.95	0.057	2.57	1.20-5.48	0.015
Brickman Index	None	1	†	1	†		
	1-299 (Light)	1.17	0.57-2.42	0.673	1.45	0.65-3.22	0.361
	300-599 (Moderate)	2.31	1.24-10.78	0.019	4.47	1.42-14.11	0.011
	600-1750 (Heavy)	4.38	1.09-17.63	0.038	4.8	1.10-20.95	0.037

†Reference category; <sup>a</sup>Adjusted for alcohol consumption, betel quid chewing and dietary pattern

**Table 4. Univariate and Multivariate Analysis of Betel Quid Chewing Habits and Risk for Oral Cancer**

Variables		Crude OR	95% CI	P	Adjusted OR <sup>a</sup>	95% CI	P
Quid chewing status	Non-chewer	1	†		1	†	
	Chewer	4.19	1.05-16.82	0.043	4.59	1.11-18.91	0.035
No of quid/day	None	1	†		1	†	
	1-10	5.32	1.03-27.52	0.046	5.97	1.08-33.04	0.041
Duration of years	None	1	†		1	†	
	>1	3.51	0.89-14.75	0.086	3.99	0.90-17.58	0.068
Type of quid	None	1	†		1	†	
	Betel leaf+ areca nut+lime+tobacco	4.19	1.05-16.82	0.043	4.74	1.13-19.89	0.033

†Reference category; <sup>a</sup>Adjusted for alcohol consumption, smoking and dietary pattern

4.59 95%CI 1.11-18.91, OR 5.97 95%CI 1.08-33.04, OR 4.74 95%CI 1.13-19.89 respectively).

## Discussion

The increasing annual rate of smokers in Indonesia is attributable to the social acceptance of the smoking habit. It is a very prevalent habit, especially among the males where initiation begins early with over a quarter of urban and rural 10-year old children already found to be smoking (Reynolds, 1999). Smoking is considered as an important sign of masculinity where men are teased and be inclined to feel "shame" if they do not smoke (Ng, 2006; Nitcher, 2009). This habit is further facilitated by the government's notably low taxation on cigarettes especially *kretek* and the minimal anti-smoking policies and regulation due to economic value of tobacco to the country (Nitcher, 2009).

This study found that *kretek* is the more commonly consumed tobacco product and its consumption is higher among the cases as compared to controls. This finding is in concordance with earlier studies where it was reported that *kretek* was the most common type of cigarette used in Indonesia (MOHRI, 2004; Achadi et al., 2005). Incorporating diverse ingredients, *kreteks* are cigarettes based on a blend of tobacco with cloves and clove oil, lending them a distinctive scent. According to folklore, the clove cigarette was first smoked to alleviate chest pain associated with asthma (Hanusz, 2000). Despite the proclaimed status of *kretek* as a key cultural signifier and traditional symbol of Indonesia, their dominance is a comparatively recent phenomenon as compared to white cigarettes which have a longer established presence.

The relationship of tobacco consumption with cancer development has been well documented. This is due to the presence of compounds such as polycyclic aromatic hydrocarbons (PAH), N-nitrosamines particularly nicotine-derived nitrosamines, aromatic amines, benzene and heavy metals, which are independently established as carcinogens for humans, in the tobacco smoke (Rodgman et al., 2000; Hoffman et al., 2001; Pfeifer et al., 2002). This study found that almost all of the smoking variables studied (smoking status, type of tobacco and pack-years of exposure of tobacco) conferred an increased oral cancer risk of at least two-fold. These findings are similar to global features of smoking worldwide (Moreno et al., 2000; Zavras et al., 2001; Lissowka et al., 2003; Subapriya et al., 2007; Muwonge et al., 2008; Javalekshmi et al., 2011). The only exception is for the number of sticks smoked per day, i.e. although those who smoked between

11-20 sticks showed an increased risk of almost three-fold, the same is not seen for those consuming more than 20 sticks. This could partly be due to the insufficient sample size in that subgroup as indicated by the wide range of the confidence interval (95% CI).

The strong association found between tobacco smoking and oral cancer in this population could also be attributable to the fact that in this study, the commonly used tobacco product is *kretek* where the addictive effect is known to be higher than conventional cigarettes. *Kretek* has been found to contain more nicotine (1.2-4.5mg), tar (46.8mg) and carbon monoxide (28.3mg) than cigarettes (1.1mg, 16.3mg, 15.5mg respectively) (Knaresborough, 1999; Malson et al., 2003). Furthermore, *kreteks* tend to be inhaled deeply due to the distinctive scent and anesthetic quality of the clove (Nitcher et al., 2009). Currently, there are very limited studies on the effect of *kretek* smoking on diseases. However a study on lung function by Bernida et al. (1990), found that the mixture of tobacco and cloves increases the temperature of cigarettes when it is burnt, thus increasing the level of carbon dioxide and nicotine to three times, as well as tar content by five times. This may confer a higher toxicity to the oral mucosa which could subsequently increase the risk for oral cancer. However, as in all studies of this nature, the compounding effect of past experiences or exposure could not be fully isolated. Therefore, it should be noted that in this study the specific role of *kretek* as an oral cancer risk indicator is difficult to be explicitly identified because of the possibility of past usage of other types of cigarette.

In Indonesia, previously because of its ancient history, betel quid chewing was considered as a socially accepted traditional culture among the elderly. However the commercialization of *kreteks* during early to mid-1990s contributes to a change in trend. Betel quid chewing is now being substituted with the smoking of *kreteks* and this is especially true among males residing in rural areas (Achadi et al., 2005). The declining trend of betel quid chewing is also seen in urban areas, for instance in the capital city of Jakarta where the prevalence of chewing has reduced significantly, even among the elderly. This is in contrast from what is seen currently in other countries such as Taiwan. The chewing of betel quid seems to be on the increase (Wang et al., 2003; Lin et al., 2004; Lin et al., 2005) where the prevalence is particularly high (46.1%) among the aborigines (Lin et al., 2006).

The betel quid consumed among Indonesians is also slightly different from the Taiwanese. Betel quid with ripe areca nut and slaked lime is chewed first, and then a

large wad of finely cut tobacco is used to clean the teeth, which is then kept in the mouth for some time. Another way is wrapping the areca nut and slaked lime in betel leaf with additions of tobacco and sweeteners or condiments. In contrast, among the Taiwanese the unripe areca nut is chewed together with slaked lime in which sometimes the betel leaf is added, however tobacco is never incorporated into the quid (Wen et al., 2005; Lee et al., 2011).

This study found that the prevalence of betel quid chewing is very low where not even one-tenth of oral cancer patients were chewing. After allowing for smoking, alcohol consumption and dietary pattern, betel quid chewers and those who chew at least one quid per day is found to have a 5-6 fold increased risk. This finding is in line with other researchers who found increased risk among current chewers and increased frequency of chewing (Balaram, et al., 2002; Muwonge et al., 2008; Javalekshmi et al., 2011). In this study the combination of betel leaf, slaked lime and areca nut with the addition of tobacco was the only quid combination practiced among the subjects.

Of interest to note, all the betel quid chewers in this study were also *kretek* smokers. This finding is in concordance with other populations where quid chewers were also found to be concurrently practicing other risk habits such as smoking and drinking (Yang et al., 2001; Wen et al., 2005; Tsai et al., 2009; Ghani et al., 2011). A study by Heck et al., (2012) found that those who chewed betel quid with tobacco had a stronger association with smoking as compared to those chewing quid without tobacco. This could be due to the fact that the chewing of quid with tobacco would supplement the nicotine intake of these patients and therefore better satisfy their addiction to nicotine. This finding is further corroborated by a study among a national Malaysian dataset which found that a history of betel quid chewing significantly increases the likelihood to start smoking (Ghani et al., 2012).

Although tobacco use either in the form of cigarettes or betel quid chewing has been recognized worldwide as significant risk factors for oral cancer, its prevalence in Indonesia especially *kretek* smoking is still very high with consumption among more than half of the adult population. This could be in part due to the fact that tobacco is the largest source of government revenue after oil, timber and gas which translate into relaxed law and freedom in advertising (Nitchter et al., 2009). Considering the established adverse effects of tobacco and areca nut on not just oral health but also an array of diseases, serious measures needs to be adopted to curb the increasing growth of the habit. Massive health education effort targeting towards the ill effects of *kretek* smoking especially, needs to be undertaken through nationwide mass media campaign. Additionally, measures such as graphical health warnings on cigarettes boxes which are currently being practiced in neighboring countries could also be implemented. However policy makers need to find ways to overcome the political and economic challenges in reducing the prevalence of tobacco consumption in view of the importance of tobacco to the country.

In conclusions, this study provides empirical support that smoking, which is positively associated with oral

cancer is the most common risk habit practiced in this study population. Similar effect of an increased risk was also seen among betel quid chewers.

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## References

- Achadi A, Soerojo W, Barber S (2005). The relevance and prospects of advancing tobacco control in Indonesia. *Health Policy*, **72**, 333-49
- Aditama TY, Pradono J, Rahman K, et al (2008). Linking global youth tobacco survey (GYTS) data to the WHO framework convention on tobacco control: the case for Indonesia. *Prev Med*, **47**, 11-4.
- Al-Attas SA, Ibrahim SS, Amer HA, Darwish Zel-S, Hassan MH (2014). Prevalence of potentially malignant oral mucosal lesions among tobacco users in Jeddah, Saudi Arabia. *Asian Pac J Cancer Prev*, **15**, 757-62.
- Amarasinghe HK, Usgodaarachchi US, Johnson NW, Laloo R, Warnakulasuriya S (2010). Betel-quid chewing with or without tobacco is a major risk factor for oral potentially malignant disorders in Sri Lanka: a case-control study. *Oral Oncol*, **46**, 297-301.
- Balaram P, Sridhar H, Rajkumar T, et al (2002). Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. *Int J Cancer*, **98**, 440-5.
- Bernida I, Yunus F, Wiyono WH, et al (1990). Faal paru dan uji bronkodilator pada perokok, bekas perokok dan bukan perokok. *Majalah Paru*, **10**, 5-11.
- Dikshit R, Gupta PC, Ramasundarahettige C, et al (2012). Cancer mortality in India: a nationally representative survey. *Lancet*, **379**, 1807-16.
- Ghani WM, Razak IA, Yang YH, et al (2011). Factors affecting commencement and cessation of betel quid chewing behaviour in Malaysian adults. *BMC Public Health*, **11**, 82.
- Ghani WM, Razak IA, Yang YH, et al (2012). Factors affecting commencement and cessation of smoking behaviour in Malaysian adults. *BMC Public Health*, **12**, 207.
- Hanusz M (2000). The history of *kretek*. Jakarta, Equinox Publishing, 140-3
- Heck JE, Marcotte EL, Argos M, et al (2012). Betel quid chewing in rural Bangladesh: prevalence, predictors and relationship to blood pressure. *Int J Epidemiol*, **41**, 462-71.
- Hoffmann D, Hoffmann I, El-Bayoumy K (2001). The less harmful cigarette: a controversial issue: A tribute to Ernst L. Wynder. *Chem Res Toxicol*, **14**, 767-90.
- IARC (2004). Betel-quid and areca nut chewing and some areca nut derived nitrosamines. In IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Lyon: IARC Press.
- IARC (1986). Tobacco smoking. In IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Lyon: IARC Press.
- Jayalekshmi PA, Gangadharan P, Akiba S, Koriyama C, Nair RR (2011). Oral cavity cancer risk in relation to tobacco chewing and bidi smoking among men in karunagappally, Kerala, India: karunagappally cohort study. *Cancer Sci*, **102**, 460-7.
- Knaresborough K (1999). Health effects of interaction between tobacco use and exposure to other agents. Geneva, Switzerland: World Health Organization.
- Krishna Rao SV, Mejia G, Roberts-Thomson K, Logan R. (2013).

- Epidemiology of oral cancer in Asia in the past decade--an update (2000-2012). *Asian Pac J Cancer Prev*, **14**, 5567-77.
- Lee CH, Ko AM, Warnakulasuriya S, et al (2011). Inter-country prevalences and practices of betel-quid use in South, South East and Eastern Asia regions and associated oral preneoplastic disorders: an international collaborative study by asian betel-quid consortium of South and East Asia. *Int J Cancer*, **129**, 1741-51.
- Lin CF, Wang JD, Chen PH, et al (2006). Predictors of betel quid chewing behavior and cessation patterns in Taiwan aborigines. *BMC Public Health*, **6**, 271.
- Lin WJ, Jiang RS, Wu SH, Chen FJ, Liu SA (2011). Smoking, alcohol, and betel quid and oral cancer: a prospective cohort study. *J Oncol*, **2011**, 525976.
- Lin YS, Chu NF, Wu DM, Shen MH (2004). Prevalence and factors associated with the consumption of betel-nut among military conscripts in Taiwan. *Eur J Epidemiol*, **19**, 343-51.
- Lin YS, Jen YM, Wang BB, Lee JC, Kang BH. (2005). Epidemiology of oral cavity cancer in Taiwan with emphasis on the role of betel nut chewing. *ORL J Otorhinolaryngol Relat Spec*, **67**, 230-6.
- Lissowska J, Pilarska A, Pilarski P, et al (2003). Smoking, alcohol, diet, dentition and sexual practices in the epidemiology of oral cancer in Poland. *Eur J Cancer Prev*, **12**, 25-33.
- Loyha K, Vatanasapt P, Promthet S, Parkin DM (2012). Risk factors for oral cancer in northeast Thailand. *Asian Pac J Cancer Prev*, **13**, 5087-90.
- Madani AH, Dikshit M, Bhaduri D (2012). Risk for oral cancer associated to smoking, smokeless and oral dip products. *Indian J Pub Health*, **56**, 57-60.
- Malson JL, Lee EM, Murty R, Moolchan ET (2003). Clove cigarette smoking: biochemical, physiological and subjective effects. *Pharmacol Biochem Behav*, **74**, 739-45.
- Ministry of Health Republic of Indonesia, Surkesnas Team (2005). National Health Survey 2004. Jakarta: Ministry of Health Republic of Indonesia, 5-22.
- Ministry of Health Republic of Indonesia (2004). The tobacco sourcebook. Jakarta: ministry of health republic of Indonesia.
- Moreno-López LA, Esparza-Gómez GC, González-Navarro A, Cerero-Lapiedra R, (2000). Risk of oral cancer associated with tobacco smoking, alcohol consumption and oral hygiene: a case-control study in Madrid, Spain. *Oral Oncol*, **36**, 170-4.
- Muwonge R, Ramadas K, Sankila R, et al (2008). Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: a nested case-control design using incident cancer cases. *Oral Oncol*, **44**, 446-54.
- Ng N, Weinehall L (2006). 'If I don't smoke, I'm not a real man'-Indonesian teenage boys' views about smoking. *Health Educ Res*, **22**, 794-804.
- Nichter M, Padmawati S, Danardono M, et al (2009). Reading culture from tobacco advertisements in Indonesia. *Tob Control*, **18**, 98-107.
- Pfeifer GP, Denissenko MF, Olivier M, et al (2002). Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene*, **21**, 7435-51.
- Reynolds C (1999) The fourth largest market in the world. *Tob Control*, **8**, 89-91.
- Rodgman A, Smith CJ, Perfetti TA (2000). The composition of cigarette smoke: a retrospective, with emphasis on polycyclic components. *Hum Exp Toxicol*, **19**, 573-95.
- Rosenquist K (2005). Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. *Swed Dent J Suppl*, **179**, 1-66.
- Schlesselman JJ (1982). Case control studies: design, conduct, analysis. New York: Oxford University Press, 105-122,171-220.
- Subapriya R, Thangavelu A, Mathavan B, Ramachandran CR, Nagini S. (2007). Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study. *Eur J Cancer Prev*, **16**, 251-6.
- Sujatha D, Hebbar PB, Pai A (2012). Prevalence and correlation of oral lesions among tobacco smokers, tobacco chewers, areca nut and alcohol users. *Asian Pac J Cancer Prev*, **13**, 1633-7.
- Tjandra YA (2006). Rokok di Indonesia. Jakarta: UI Press, 3.
- Tsai KY, Su CC, Lin YY, Chung JA, Lian IB (2009). Quantification of betel quid chewing and cigarette smoking in oral cancer patients. *Community Dent Oral Epidemiol*, **37**, 555-61.
- Wang SC, Tsai CC, Huang ST, Hong YJ (2003). Betel nut chewing and related factors in adolescent students in Taiwan. *Public Health*, **117**, 339-45.
- Wen CP, Tsai SP, Cheng TY, et al (2005). Uncovering the relation between betel quid chewing and cigarette smoking in Taiwan. *Tob Control*, **14**, 16-22.
- Wynder EL, Bross IJ (1957). Aetiological factors in mouth cancer; an approach to its prevention. *Br Med J*, **1**, 1137-43.
- Yang YH, Lee HY, Tung S, Shieh TY (2001). Epidemiological survey of oral submucous fibrosis and leukoplakia in aborigines of Taiwan. *J Oral Pathol Med*, **30**, 213-9.
- Zavras AI, Douglass CW, Joshipura K, et al (2001). Smoking and alcohol in the etiology of oral cancer: gender-specific risk profiles in the south of Greece. *Oral Oncol*, **37**, 28-35.
- Znaor A, Brennan P, Gajalakshmi V, et al (2003). Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer*, **105**, 681-6.