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## MINI-REVIEW

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# Prevention of Betel Quid Chewers' Oral Cancer in the Asian-Pacific Area

Itsuo Chiba

### Abstract

“Betel quid chewers' oral cancer” is one of the most common malignancies in South and Southeast Asian countries. Oral premalignancies are also very common in betel quid chewers and about 10% of these undergo malignant transformation. Although education for cessation of the betel quid chewing habit is important, there are few adequate strategies and policies for primary prevention, health promotion and education related to oral cancer control, especially in rural areas. In addition to oral health education, it is also crucial to establish a data-management system as well as monitoring and evaluation systems for oral cancer prevention.

**Key words:** betel quid - oral cancer - premalignancy - prevention - genetic changes

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## 1. Epidemiological Background

### Introduction

Oral cancer is one of the most common cancers in South and Southeast Asian countries, in contrast to accounting for only 1 to 4% of the total malignant tumors in Western societies (Field and Spandidos, 1987). The age-adjusted rates of oral cancer incidence are 24.2/100,000 for males and 11.2/100,000 for females in Kerala, India (Nair et al., 1988) and 10.2/100,000 for males and 4.1/100,000 for females in Sri Lanka (Randeniya, 1987). There are strong indications for an association of the habit of betel quid chewing with cancers of the mouth, oropharyngeal cavity, and upper parts of the digestive tract (Dave et al., 1992; Jayant et al., 1977; IARC Monograph, 1985). Moreover, chewing and smoking habits interact synergistically for these cancers (Jayant et al., 1977). Although some pathological (Pindborg, 1980), epidemiological (Boyle et al., 1990; Gupta et al., 1996; Hirayama, 1966; Mehta et al., 1981) and genetic (Chiba et al., 1998; Kashiwazaki et al., 1997) studies on oral cancer and precancer have been already reported, the incidence of oral cancer is still very high in these countries and only limited efforts have been carried out for its

prevention (Boyle et al., 1990).

The objectives of this paper are to review 1) the habit of betel quid chewing, 2) oral lesions caused by the habits, 3) the molecular events in the oral mucosa of the betel quid chewers and 4) oral cancer prevention trials and policies in the Asian-Pacific area.

### Betel Quid Chewing Habits

Oral cancer was described in the Sushruta Samhita, a treatise on Indian surgery written in Sanskrit around 600 B.C. In addition, literary references to the habit of chewing betel quid (betel leaf, areca nut and lime) in India are at least 2,000 years old. Tobacco was introduced around the sixteenth century. It is estimated that at least 200 million individuals consume areca nuts in one form or another worldwide. The habit is now widespread in Southeast Asia and the South Pacific islands (Figure 1) and in people of Indian origin elsewhere in the world. The betel quid chewing habit is in fact found all over the world wherever Indians have settled.

There is some confusion in the reporting of “betel quid” and tobacco chewing habits. At a recent workshop in Kuala Lumpur (Zain et al., 1997; Zain et al., 1999), it was

*Itsuo Chiba, D.D.S., Ph.D., A.O.S.(Jpn), Oral Diagnosis and Oral Medicine, Oral Patho-biological Science, Hokkaido University Graduate School of Dental Medicine, Kita-13, Nishi-7, Kita-ku, Sapporo 060-8586, Hokkaido, Japan Tel & Fax: +81-11-706-4280, e-mail: ic@den.hokudai.ac.jp*



**Figure 1. Gray Areas Demonstrate Regions which have Betel Quid Chewing Habits in Southeast Asia and the South Pacific Islands (So far, it is not yet confirmed betel quid chewing in Madagascar in the literature). In Addition to these Countries, there are many Countries where People of Indian Origin with the Habit live.**

recommended that “quid” be defined as “a substance, or mixture of substances, placed in the mouth or chewed and remaining in contact with the mucosa, usually containing one or both of the two basic ingredients, tobacco and/or areca nut, in raw or any manufactured or processed form.”

There are several types of chewing habits in India featuring use of betel quid (fresh betel leaf, fresh areca nut, slaked lime, catechu and tobacco), pan masala (areca nut, slaked lime, catechu, condiments and tobacco), mainpuri (tobacco, slaked lime, areca nut, camphor and cloves), mawa (areca nut, tobacco and slaked lime), khaini (tobacco and slaked lime), gutka (an industrially manufactured food item) and other smokeless tobaccos (mishri, gudhaku, bajjar etc.).

In Sri Lanka, the betel quid is composed of fresh betel leaf, fresh areca nut, slaked lime and tobacco, and they are introduced together inside the mouth.

In Papua New Guinea, betel quid chewing is practised in a different way as compared to the rest of Southeast Asia. Areca nut, betel leaf and slaked lime are introduced into the oral cavity separately; however, tobacco is never included in these preparations (IARC Monograph, 1985).

There are many reasons for chewing betel; it causes euphoria, increases salivation, satisfies hunger, relieves tooth pain and ameliorates nausea in pregnant women. Because of these reasons, it is very difficult to persuade people to quit betel quid chewing.

## 2. Carcinogens in Betel Quid Ingredients

The major areca nut alkaloids are arecoline, arecaidine, arecolidine, guvacoline and guacine (IARC Monograph, 1985). Arecoline (1,2,4,5,-tetrahydro-1-methyl-

pyridinecarboxylic acid; molecular weight 155.19) is the most abundant alkaloid of areca. These alkaloids undergo nitrosation and give rise to N-nitrosamines (Hoffmann et al., 1994). It has been suggested that metabolic activation may involve the cytochrome p450 system (Sundqvist et al., 1991; Wary and Sharan, 1991). The nitrosation of arecoline may produce a variety of betel quid-specific nitrosoamines (BQSN). The BQSN interact with DNA, proteins or other targets forming adducts to exert its carcinogenic activity.

The introduction of tobacco from European countries reinforced this practice, and now almost all habitually chewed betel quids include tobacco. A comparison of the carcinogenicity of the habit of chewing betel quid with and without tobacco has been attempted through a reassessment of the available epidemiological evidence on the aetiology of oral cancer and pre-cancer; however, the role of tobacco use in the carcinogenicity of betel chewing is still unclear (Gupta et al., 1982). Analytical studies should clearly distinguish between chewing habits with tobacco and without tobacco.

Slaked lime is also included in betel quid. It causes inflammation in the submucosal area and Nair et al. have reported that the calcium hydroxide content of lime in the presence of the areca nut is primarily responsible for the formation of reactive oxygen species that might cause oxidative damage in the DNA of buccal mucosa cells of betel quid chewers (Nair et al., 1990).

In addition to these ingredients of betel quid, tooth attrition caused by the chewing action is also important for the establishment and development of oral cancers. The oral mucosa could thus be injured by the keen edges of teeth resulting in facilitated exposure and regeneration.

### 3. Oral Lesions Caused by Betel Quid Chewing

Oral cancer occurs more commonly among men than women depending upon the extent and type of tobacco habits prevalent. Betel quid chewing is the major risk factor for buccal mucosal and gingival cancer. For the tongue cancer most frequent in Western countries smoking is the major risk factor.

Leukoplakia is one of the commonest lesions in betel quid chewers. The WHO has classified these into two groups, homogeneous and non-homogeneous. Among non-homogeneous leukoplakias, nodular leukoplakia tends to show the highest rate of malignant transformation. The relative risk compared with individuals with tobacco habits but without any precancerous oral lesion was also found to be the highest for nodular leukoplakia (Gupta et al., 1989).

Oral submucous fibrosis (OSMF) is a chronic condition characterized by mucosal rigidity of varying intensity due to fibroelastic transformation of the juxta-epithelial layer (Murti et al., 1995). OSMF is a high-risk precancerous condition (Pindborg et al., 1984) with a malignant transformation rate of about 7.6% (Murti et al., 1985). Areca nut chewing could be one of the most important etiologic factors in OSMF (Sinor et al., 1990).

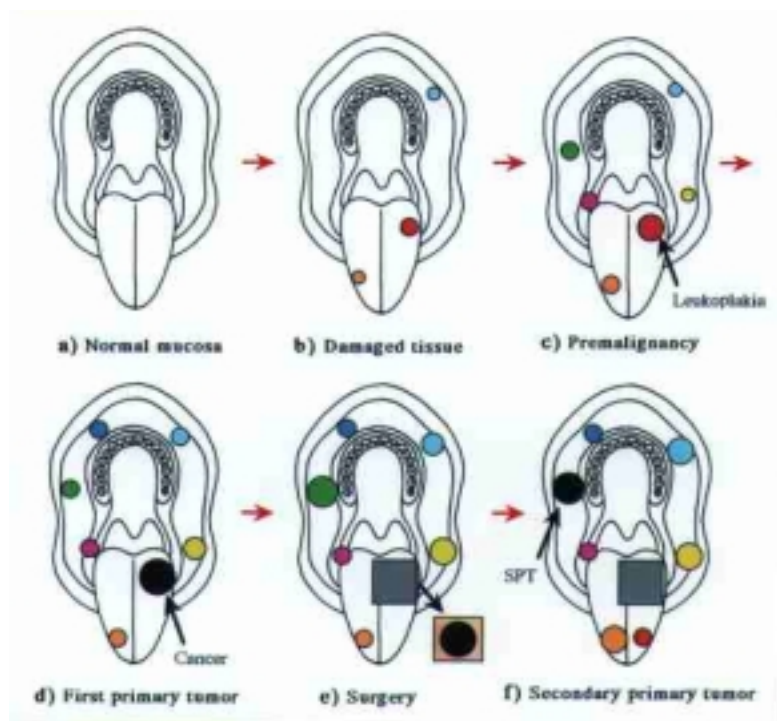
Oral lichen planus may be important for malignant transformation, although its nature remains unclear (Murti et al., 1986). It has been categorized as a "probable precancerous condition (Mehta and Hamner, 1993)."

### 4. Genetic Alterations

Little is known of the genetic events involved in the progression of precancerous status to oral cancer (Pillai et al., 1991). Moreover, most molecular studies have been performed on populations from developed countries in which the rates of incidence of oral cancers are relatively low. Genetic events related to betel quid chewing have, however, been reported for some genes.

#### *p53* gene

Results of immunohistochemical analysis of p53 are controversial. Some researchers have reported p53 expression in oral cancer of betel chewers (Kaur et al., 1994; Kuttan et al., 1995; Ranasinghe et al., 1993). p53 expression could be correlated with malignant potential of precancers and prognosis; however, there are some reports that there is no significant relationship with their likelihood of malignant transformation (Murti et al., 1998). Rather than immunohistochemistry, mutational analysis of the p53 gene using PCR-SSCP, a yeast functional assay and sequencing is informative (Kashiwazaki et al., 1997). Using these methods, we detected mutations in 43% of oral cancers in betel quid chewers in Sri Lanka (Chiba et al., 1998). Moreover, these mutations were clustered in exon 5, suggesting that this site could be one of the specific targets for some carcinogens in betel quid ingredients (Chiba et al., 1998).



**Figure 2. a) There are no Phenotypic and Genetic Changes in Normal Mucosa. b) Damaged Tissue is Phenotypically Normal but Genetically Affected. c) Accumulation of Genetic Changes Results in the Appearance of a Premalignant Lesion Surrounded by "Damaged Tissue". d) The First Primary Cancer has Appeared. Accumulation of Genetic Changes is Continuing Around the Cancer. e) Surgical Excision was Performed. f) Secondary Primary Cancer Appears from Damaged Tissue.**

*Ras Genes*

Mutations in the H-ras gene are more frequent in oral cancers of betel quid chewers (Saranath et al., 1991) than those in Western countries (Chang et al., 1991; Warnakulasuriya et al., 1992; Xu et al., 1998; Yeudall et al., 1993) and Japan (Matsuda et al., 1996; Sakai et al., 1992; Sakata, 1996). Ki-ras mutations have also been reported in oral cancers of betel quid chewers in Taiwan (Kuo et al., 1994). These observations suggest that there are genetic and etiological differences in oral cancers between populations from these geographical areas.

*Field Cancerization*

In 1953, Slaughter et al. (Slaughter and Southwick, 1953) demonstrated “field cancerization” from the pathological point of view. Chronic exposure to alcohol and tobacco causes field cancerization. This concept should be considered in molecular biological studies of oral cancer (Figure 2). Waridel et al. (Waridel et al., 1997) reported that multiple biopsies of histologically normal tissue from the upper aero-digestive tract were tested and clonal p53 mutations were identified in 76% (38/50) of biopsies from patients presenting with multiple tumours compared with 32% (38/117) of biopsies from patients presenting with single tumours. Jang et al. (Jang et al., 2001) reported that lesions in the majority of multiple oral cancers and precancers arise from clonally independent cells affected by field cancerization. “Normal” oral mucosa as well as the precancer or cancer of betel quid chewers could be genetically affected by betel quid ingredients.

*Glutathione-S-Transferases and Cytochrome p450s*

Molecular epidemiological examinations have provided evidence that oral cancer susceptibility is also mediated by genetic and epigenetic factors. Although betel quid chewing is clearly established as the main risk factor for oral cancer, only a small proportion of betel quid chewers develop significant lesions, suggesting the presence of inherited differences in the genes of enzymes which detoxify or

activate carcinogens. Glutathione S-transferases (GSTs) are involved in detoxification of carcinogens and homozygous deletions are associated with higher risks of cancer.

Homozygous deletion of the GST  $\mu$  class isozyme (GSTM1) gene has been shown to occur in approximately 50% of populations of various ethnic origins (Kiyohara, 2000), while homozygous deletion of the GSTT1 gene occurs in between 10 and 64% in various ethnic groups. In oral cancers, an increased risk for developing premalignancies in null genotypes of GSTM1 and T1 has been reported (Nair and Bartsch, 2001; Nair et al., 1999).

Cytochrome p450s regulate the expression of enzymes that convert procarcinogens to their ultimate carcinogenic forms (Sundqvist et al., 1991; Wary and Sharan, 1991). The nitrosation of arecoline, which contains a 3- ethylenic bond at the 3-4 position on the pyridinium ring, may produce a variety of betel-nut-specific nitrosoamines (BSNA). Although cytochrome p450 CYP2D6, CYP1A1 and CYP2E1 loci have been examined for oral cancer patients and control individuals, there are no differences between them in the frequencies of presumed risk genotypes (Matthias et al., 1998). Recently, our group demonstrated that deficient CYP2A6 activity due to genetic polymorphism reduced oral cancer risk in betel quid chewers in Sri Lanka (Topcu et al., submitted).

**5. Oral Cancer Prevention Trials in Asia**

*Primary Prevention*

Intervention studies for primary prevention of oral cancer in India by Gupta et al. have been very enthusiastic (Gupta, 1991; Gupta et al., 1989; Gupta et al., 1986; Gupta et al., 1992; Gupta et al., 1990; Gupta and Mehta, 2000; Gupta et al., 1995).

Randomized intervention trials to evaluate oral visual inspection for the early detection and prevention of oral cancer started from 1986 in India. Trained health workers identify, recruit, examine and refer subjects with suspected lesions for confirmation and management (Mehta et al.,

**Table 1 Socio-economic Status in Sri Lanka (1997)**

Occupational group	Mean monthly income (US\$)		
	1986/87 Nominal	1996/97 Nominal      Real	
Professional, technical and related workers	33.3	96.0	29.6
Administrative and managerial workers	105.5	282.0	86.9
Clerical & related workers	27.5	84.7	26.1
Sales workers	35.2	96.9	29.8
Agriculture, animal husbandry, forestry workers and fishermen	13.4	38.1	11.8
Production & related workers, transport equipment operators & labourers	18.1	61.3	18.9
Workers not classified by occupation	13.1	40.6	12.5
<i>Key economic indicators</i>			
Unemployment rate, % of labour force:		10.3%	
Inflation: change of Colombo consumers' price index:		9.6%	
Per capita GNP, US\$		804	

1986). Subjects with confirmed oral precancers are advised to quit using tobacco, and encouraged to undergo removal of excisable non-homogeneous oral leukoplakias, if present.

A total of 36,471 tobacco chewers and smokers were selected from the rural population (Gupta et al., 1986). People in the intervention cohort were encouraged to give up their habits by personal advice and via the mass media. No educational intervention was provided to the control cohort.

A reduced incidence of oral pre-cancerous lesions was reported after a primary prevention trial for 12,212 betel quid chewers and smokers was carried out (Gupta, 1991; Gupta et al., 1992).

#### *Chemoprevention*

A randomized intervention trial to evaluate the cancer preventive potential of vitamin A in subjects with non-homogeneous oral precancerous lesions in Kerala, India, has been performed (Stich et al., 1989; Stich et al., 1988; Stich et al., 1988). Short-term administration of vitamin A is effective for oral precancer as the lesions were reversed; however, severe side effects were detected. A study involving supplementation of multiple micronutrients to 169 subjects with OSMF in Karachi, Pakistan, resulted in a significant relief of symptoms such as intolerance to spicy food, burning sensation, and difficulty in mouth opening, was observed (Maher et al., 1997).

## **6. Oral Cancer Prevention Policy in Asia for 21st Century**

#### *Socioeconomic Background*

Consideration of the socioeconomic background is highly important in developing a prevention strategy for oral cancer as it is closely related to lifestyle and behavior (Gupta, 1996). The average monthly income was from 200 to 300 Rs. (\$2 to 3) in rural areas of Sri Lanka (Ratnapala, 1989). Recent economic status was shown in Table 1 (Sri Lanka Socio-Economic Data 1998; Report on Consumer Finances and Socio Economic Survey 1996/1997 Part 1, 1999). In our survey, around half of the betel quid chewers consisted of farmers or estate labourers in these areas. The cost of a betel quid is only 5 Rs. for these inhabitants, which makes betel quid chewing preferable to cigarette smoking (7.5 to 10 Rs. per cigarette). Beedi (or bidi), which is made by rolling a dried, rectangular piece of the temburni leaf into a conical shape containing a small amount of finely cut tobacco, is very popular and cheap (50 cents) in India, Sri Lanka and other Southeast Asian countries. Both betel quid and beedi are life-threatening habits for low income people.

The access of the people living in rural areas to hospitals is limited because of a number of reasons; besides the money concern, it may also be risky for keeping a job, a trouble that reflects upon the entire family.

#### *Policies for Oral Cancer Control*

A 'well-managed' national oral cancer control program

should be formulated in each country. Adequate strategies and policies for primary prevention, health promotion and education related to oral cancer control should be developed based on quantitative and qualitative information on the behavior and lifestyle of the population and their sociocultural and economic background together with longitudinal monitoring. For example, The Regional Cancer Center, in the city of Trivandrum, Kerala, India, has a comprehensive oral cancer research program to provide leads for control of oral cancer (Sankaranarayanan et al., 1992). This type of program should be carried out as a national project. A cancer registry should be compiled based upon the data from all facilities that conduct cancer therapy. It is important to establish a data-management system as well as monitoring and evaluation systems. Oral cancer control strategies should take into account environmental and cultural factors in order to change the lifestyle and behavior of the high risk population.

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### Personal Profile: Itsuo Chiba

Dr Itsuo Chiba is presently senior lecturer in the Graduate School of Dental Medicine at Hokkaido University. After graduating from this university in 1987, he became a researcher in the Laboratory of Pathology, Cancer Institute, Hokaido University School of Medicine, then spending two years in the National Institutes of Health, Maryland in the USA, before returning to Hokkaido and the First Department of Oral Surgery. Since 2000 he has been very active as a JICA expert for the Dental Education Project at the University of Peradeniya in Sri Lanka: the title is 'Strengthening Diagnosis and Epidemiological Survey Capacity and Collaboration Research'.

Dr Chiba is pictured below (far right), together with Sri Lankan colleagues in the oral cancer prevention team, Mr Sarath Fernando, Dr Malsantha Muthumala and Mr Vasantha Muthumala (from left to right).

