

A Study of 63 Cases of Mouth Neoplasms in Arecanut Growing Belt of Sullia

Naik SM¹, Naik SS²

Abstract

Background: Betel nut and betel quid chewing are from major etiological factor for oral cancer. They also increase the risk of systemic diseases such as asthma, diabetes mellitus, metabolic syndrome, myocardial infarction, hypertension, and other cardiovascular diseases.

Methods: Sixty three patients of oral cancer in our institution during Jan. 2007 to May 2011 were included in our study. This study included 14 cases of lip carcinoma, 41 cases of buccal mucosa carcinoma, 7 cases of tongue carcinoma, and 1 case of carcinoma of upper alveolus. Duration of use of betel quid, pan masala, and gutkha were studied as well as management.

Results: All patients in our study have been chewing betel-quid for 6-31 years (mean 19.42 years). All of them quit betel quid and used easily available panmasala and gutkha for 4-13 years (mean 8.28 years). Nine cases of lip carcinoma, 13 cases of buccal mucosa carcinoma and 3 cases of tongue carcinoma were treated with surgery. Seven cases of lip carcinoma, 30 cases of buccal mucosa carcinoma and 5 cases of tongue carcinoma were treated with post operative or palliative radiotherapy.

Conclusion: Betel nut chewing with or without tobacco and lime are proven to be carcinogens in human. Direct relationship between oral cancer and betel quid, gutkha, and panmasala use has been shown in our study. As betel quid, panmasala and gutkha chewing were proven to be carcinogens, a permanent ban on manufacturing and sale of these products should be implemented.

Keywords: Areca; Mouth neoplasm; Tobacco; Smoking

Please cite this article as: Naik M Sudhir, Naik S Sarika. A Study of 63 Cases of Mouth Neoplasms in Arecanut Growing Belt of Sullia. *Iran J Cancer Prev.* 2012; 5(1): 39-45.

1. Dept. of ENT, Head and Neck Surgery, KVG Medical College, Sullia, India
2. Dept. of Anesthesia, KVG Medical College, Sullia, India

Corresponding Author:
Sudhir M Naik, MBBS, MS
Associate Professor of ENT
Tel: (+91)99 16 80 71 09
Email: sud223@gmail.com
Received: 18 Oct. 2010
Accepted: 18 Sep. 2011
Iran J Cancer Prev 2012; 1:39-45

Introduction

Use of betel nut and betel quid are well known in history of India [1]. The association of this habit with oral cancer was noted over a century ago; yet the chewing of betel quid in India was considered to be a comparatively innocuous practice with complete socio-cultural acceptance [1]. In recent years it has emerged as a significant public health problem in India [1]. The normal cultural practice of betel nut ended up to a health hazard when tobacco was introduced by the European settlers four centuries ago [1]. In addition to its use for smoking, as the Europeans demonstrated, tobacco somehow got mixed with betel quid and prepared to be chewed [1]. In India tobacco was culturally accepted as it was used with a culturally accepted betel quid substance [1].

During the second half of the 20th century, the causal association between chewing of betel quid with tobacco and oral cancer was well established, so it could no longer be regarded as a completely innocuous practice [2]. The major culprit was clearly tobacco in the quid; however, probably because of its 'exotic' appeal, areca nut was erroneously thought of as playing a more important role [3]. Betel nut was reported safe in many studies where only tobacco in the quid was held responsible for oral cancers [4]. Later it was clear that betel nut chewing was responsible for Oral Submucous Fibrosis (OSMF), an established precancerous condition with trismus [5].

OSMF was a rare disease in the early 80's, occurring generally among older age groups who chew betel quid frequently [6]. A later incidence of OSMF increased amongst the Indian young



Figure 1. Panoramic view of x-ray mandible showing infiltration of the left 3 molar



Figure 2. Betel leaves and betel quid (pan) being prepared.



Figure 3. Gutkha being sold and anti cancer propaganda on gutkha.



Figure 4. Oral submucous fibrosis

population as a result of increasing gutkha chewing [6]. The frequency of oral cancer has increased among young adults as a result of increasing number of OSMF (a precancerous condition) [7]. The increasing incidence of OSMF and oral cancers during the last two decades was due to industrial manufacturing and marketing of these chewable mixtures gutkha [7]. The younger generations were targeted with multimedia advertising [7].

The incidence of oral cancer is 12.5/100,000 and the largest numbers of oral cancer patients are present in India [8]. In India, oral cancer includes 9.4

percent of all cancers [8]. This epidemic proportion of oral cancer in India is due to the rampant use of betel nut, betel quid, and gutkha and pan masala chewing which are proven to be carcinogens [8]. Oral cancer is uncommon disease in the West but continue to be the major cause of cancer related death in Indian men [8]. Over last few decades, large funds have been spent to educate public, implement laws effectively, rehabilitate tobacco growers, build cessation facility, create health care infrastructure, etc to reduce the betel nut, betel quid,



Figure 5. Carcinoma of the buccal mucosa with lymph node metastasis



Figure 6. T4 carcinoma of the buccal mucosa and tongue



Figure 7. Carcinoma of the upper alveolus due to chewable raw tobacco



Figure 8. Post operative radiotherapy in carcinoma of the buccal mucosa

gutkha and other forms of chewable tobacco usage [8].

Materials and Methods

This is a retrospective study of 63 cases of oral cancer patients who were managed in KVG Medical College Sullia. The study was conducted during January 2007 and May 2011. Sixty three patients, 38 males and 25 females, were included in our study. The youngest patient was 47 years old and the oldest was 73. A detailed history of the patients

was taken plus oral and oropharyngeal examination. Baseline investigations were done along with routine blood and urine examinations.

Chest x-ray along with AP neck x-ray, lateral view and panoramic view were taken (Figure 1). The biopsy of the ulceroproliferative mass was taken; histopathology of all specimens showed squamous cell carcinoma. TNM staging (Tumor size, Lymph nodes, Metastasis) showed most of the cases were in advanced stages.

All of 63 patients were managed according to the oral cancer management protocol and all signed written informed consent.

All patients aged 47-73 (mean 61.67) years. The mean age in males was 61.20 years and female median age was 59.92 years. The mean duration of betel chewing in males was 18.56 years and in females was 20 years (Figure 2). All patients in our study changed to chewing packaged panmasala and gutkha which were easily available. The mean duration of panmasala and gutkha chewing in males was 8.66 years and in females was 7.36 years (Figure 3).

Thirteen males (mean 11.2 years) in our study were tobacco smokers and 12 males (mean 9.4 years) were occasional alcohol drinkers. Twelve males (mean 10.3 years) and 14 females (mean 8.4 years) were workers in tobacco processing industry.

Ischemic heart disease and hypertension were seen in 22 patients (16 males and 6 females). Diabetes mellitus was seen in 11 cases (4 females, 7 males). No other malignancies were seen in all cases. Thromboangiitis obliterans were seen in 15 male patients. Oral submucous fibrosis and leukoplakia were excluded from the study after histopathological examination (Figure 4).

Out of 63 cases, 14 had lip carcinoma, 41 with carcinoma of the buccal mucosa and 7 had carcinoma of tongue and there was 1 case of carcinoma of upper alveolus. Out of 14 cases of carcinoma of lip, 2 cases were in stage 1, 3 cases in stage 2, 7 cases in stage 3, and 2 cases in stage 4.

Out of 41 cases of buccal mucosa carcinoma, 4 were in stage 1, 11 in stage 2, 18 in stage 3, and 8 cases in stage 4 (Figure 5). Out of 7 cases of tongue carcinoma, 2 were in stage 1, no cases in stage 2, 2 cases in stage 3, and 3 cases in stage 4 (Figure 6). The case of carcinoma of upper alveolus refused treatment and was lost in follow up (Figure 7).

Results

All Stage 1 oral cancer patients in our study were treated by wide excision only and followed up for 6 months to 2 years. Three cases of lip carcinoma with stage 2 were treated by wide excision and postoperative radiotherapy (Figure 8). Two cases of buccal mucosa carcinoma with stage 2 were widely excised and were sent for postoperative radiotherapy, 8 patients were sent for radiotherapy as they refused surgery and 1 refused radiotherapy (Table 1). Out of 7 cases of lip carcinoma with stage 3, 3 patients refused treatment and 4 had wide excision with neck dissection and postoperative radiotherapy.

Out of 18 cases of carcinoma of buccal mucosa stage 3, 7 patients underwent wide excision with neck dissection plus radiotherapy, 11 refused surgery so they were referred to radiotherapy. One case of carcinoma stage 3 had wide excision with radiotherapy and the other refused surgery but took radiotherapy. Two cases of lip carcinoma with stage 4 refused surgery so they were given radiotherapy. All buccal mucosa carcinoma patients with stage 4 refused surgery but only 2 of them received radiotherapy. All 3 cases of tongue carcinoma with stage 4 refused both surgery and radiotherapy. All patients were followed up every month.

A direct relation between oral cancer and duration of betel quid, gutkha and panmasala chewing was seen in our study. The incidence was earlier if the patient was alcoholic and smoker.

Discussion

Betel nut may be consumed alone or as a betel quid in combination with betel leaf and slaked lime and may contain other substances like tobacco, catechu, spices or sweeteners [9, 10]. Betel leaf that is commonly consumed with this nut contains a known carcinogen named safrole [9, 10]. The lime in the betel quid enhances the extraction of the betel nut alkaloids by salivary degradation and promotes carcinogenesis [9, 10]. The alkaloids in betel nut which are responsible for the biological actions in humans are arecoline, arecaidine, guvacine, and guvacoline [9, 10]. Asians and Indians even after immigrating to western countries still continue the habit of betel nut chewing which show an addiction among these populations [9, 10].

The betel nut derived alkaloids are cholinergic agonists and they affect nervous system via acetylcholine [11]. Prolonged use of betel nut causes peculiar facial and systemic features, staining of teeth, attrition of teeth, and creation of wear facets with higher incidence of periodontitis [11]. Betel nut for consumption is obtained from areca catechu which is the fourth most common addictive substance after tobacco, alcohol, and caffeine. It has 600 million users in the world [12]. It is possibly the second most consumed carcinogen after tobacco in the Indian subcontinent [12].

In India, betel nut is chewed for variety of reasons such as stress reliever, mouth freshener, improving concentration, and for digestion after food [13]. Addiction withdrawal symptoms are mood swings, anxiety, and irritability, loss of concentration, sleep disturbance and craving which were seen in most cases in our study [14]. Betel nut psychosis has been reported in heavy users following sudden cessation

Table 1. Incidence and management of carcinoma of the oral cavity

Stage	Carcinoma of lip	Carcinoma of buccal mucosa	Carcinoma of tongue	Total
1	2 cases	4 cases	2 cases	8 cases
	2 wide excision done	4 wide excision done	2 wide excision done	
2	3 cases	11 cases	0 cases	14 cases
		1 refused treatment		
	3 wide excision + radiotherapy	8 sent for radiotherapy as they refused surgery		
		2 wide excision and post – op radiotherapy		
3	7 cases	18 cases	2 cases	27 cases
	3 refused treatment	11 refused surgery so radiotherapy	1 wide excision + radiotherapy	
	4 wide excision + neck dissection with radiotherapy	7 wide excision + neck dissection with radiotherapy	1 refused surgery so radiotherapy	
4	2 cases	8 cases	3 cases	13 cases
	2 refused treatment so radiotherapy	6 refused treatment	3 refused surgery and radiotherapy	
		2 refused surgery so radiotherapy		
Total	14 cases	41 cases	7 cases	62

of the habit [14]. India is the greatest producer of betel nut something like 330,000 million tonnes per year (nearly half of global betel nut production) [13].

The total area under betel nut cultivation in India is estimated to be around 372,000 hectares and total production is 340,000 tonnes [13]. It is estimated that nearly 10 million people depend on betel nut industry for their livelihood in India [13]. Most of the betel nut production is consumed within India because it has limited export potential [13]. Betel nut products (gutkha, panmasala) are being advertised as mouth fresheners which are misleading Indian youth [15].

Gutkha and panmasala are more dangerous than betel nut alone because they are kept in mouth for a longer time [13]. The other promoting factors in this industry are lack of statutory warning, low cost, easy availability, attractive packaging and aggressive marketing [13]. This has increased new generation of users who are innocent adolescents and youth [13]. Panmasala is basically a preparation of betel nut, catechu, cardamom, lime and a number of natural, artificial perfuming and flavoring materials [16]. Gutkha is a variant of panmasala, in which in addition to these ingredients flavored chewing tobacco is added. Both products are often sweetened to enhance the taste [16]. Betel leaf is perishable and preparation of betel quid is somewhat complex or requires visits to shops selling Pan/BQ. With the emergence of commercial pan

masala and gutkha about three decades ago, not only did the Indian market witness massive growth in the sales of smokeless tobacco and betel nut products, but also a huge worldwide export market developed [16,17]. All our patients earlier chewed betel quid but turned to gutkha, pan masala chewing over the last two decades.

Just like tobacco, betel nut is a psychostimulant, an addictive substance and a carcinogen [13]. The cancer causing properties of betel nut have been well-reported in animal, human and epidemiologic studies [13]. Cancers caused by betel nut chewing also shows a strong dose–response relationship for frequency and duration of chewing [13]. N-nitroso compounds converted from betel nut alkaloids are responsible for oral and pharyngeal cancer [13]. Also betel nut chewing (with or without tobacco) is associated with hepatocellular carcinoma, cholangiocarcinoma, cancers of the larynx, stomach, lung and cervix in humans [13]. Betel nut is a synergistic carcinogen along with tobacco with which it is commonly consumed in India [13]. All patients in our study had betel quid and gutkha panmasala chewing as the etiology with smoking, alcohol consumption and working in tobacco processing factories as other etiologies.

The WHO and International Agency for Research on Cancer classified betel nut as a Group 1 human carcinogens with sufficient evidence of increased risk of OSMF (precancerous oral lesion) and cancers of

the oral cavity, pharynx and esophagus [17-20]. Cancers caused by betel nut chewing also shows a strong dose-response relationship for frequency and duration of chewing [18]. It is postulated that betel nut-specific N-nitroso compounds converted from alkaloids are responsible for oral and pharyngeal cancer [18]. There are several other reports that have linked betel nut chewing (with or without tobacco) with hepatocellular carcinoma, cholangiocarcinoma, laryngeal cancers, stomach, lung and cervix in humans [18].

Studies in mice have shown that, betel quid extract given by gavages produced carcinoma of lung, stomach, liver and salivary gland [18]. Fibrosarcomas at the injection site were observed by subcutaneous injections of betelnut extracts in mice [18]. Animal research has shown that panmasala in the diet led to tumors in various organs, most frequently adenocarcinoma of lung [18]. In another experiment, Arecoline was given as gavage and it produced carcinoma of lung, stomach and hemangiomas of liver [18]. Esophageal cancers increased 195 times, pharyngeal cancers 96.9 times and laryngeal cancers 40.3 times when betel quid chewers had habits of smoking and drinking [21]. Fortunately none of our patients had synchronous cancers. Betel quid chewing resulted in a statistically significant increase in the risk of overall mortality and cerebrovascular deaths in the elderly population [22, 23].

Betelnut addiction has also been found to be associated with heart attacks, arrhythmia, metabolic syndrome and diabetes [24-27]. There are reports of acute exacerbation of asthma and hypertension in betel nut chewers [28]. Chronic betel nut chewers' women give birth to low weight babies similar to smoker women [29, 30]. Betel nut and betel quid chewing has been a popular oral habit in India and many other Southeast Asian countries for a long time [31, 16]. Betel nut, betel quid and gutkha chewing habit has become the top five oral habits (including smoking, alcohol, tea, coffee, and betel chewing) in the world. There are about 200-600 million betel nut, betel quid and gutkha chewers in the world [28, 29]. They are proven carcinogens resulting in oral cancer, oral precancerous lesions, hepatocarcinoma, diabetes mellitus (DM), cardiovascular diseases and other systemic diseases [31, 16].

India accounts for 1/3 of an estimated 3 million betel and tobacco related deaths in the world per year [16]. In 2001, the sale of cigarettes was banned to people under 18 [16]. In view of high usages of betel nut, betel quid and other tobacco containing products such as gutkha and their proven

role as a carcinogen, it is necessary to look into the hazardous effects of these addictions and their impact on health and society [16]. So a ban on betel nut, betel quid and tobacco in any form is immediately necessary to eradicate the menace of the morbidity [16].

Conclusion

Panmasala and gutkha have flooded the Indian market as cheap and convenient betel quid substitutes and become popular across all age groups wherever betel nut is abundantly used. There is sufficient evidence that chewing of betel nut with or without tobacco and lime are carcinogenic in humans.

Some restrictions on the manufacture and sale of these products are being implemented but because of seriousness of the situation, a permanent ban on gutkha and panmasala is necessary as they are well-established oral cancer causing agents. An emphasis on health education aiming to reduce and later eliminating betel nut and tobacco products should be placed.

Acknowledgement

The support from KVG Medical College, Sullia is gratefully acknowledged.

Conflict of Interest

The authors have no conflict of interest in this article.

Authors' Contribution

SMN designed the study, analyzed the data and wrote the paper. SSN contributed to data entry, literature review, writing up process, study design and analysis.

References

1. Reddy KS, Gupta PC. Report on Tobacco Control in India. Ministry of Health and Family Welfare, Government of India: New Delhi; 2004.
2. Control of oral cancer in developing countries. A WHO meeting. Bull World Health Organ 1984; 62:817-30.
3. Gupta PC, Pindborg JJ, Mehta FS. Comparison of carcinogenicity of betel quid with and without tobacco: An epidemiological review. Ecol Dis 1982; 1(4):213-9.
4. International Agency for Research on Cancer: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 37, Tobacco Habits other than Smoking; Betel-quid and Areca-nut Chewing; and some related Nitrosamines. International Agency for Research on Cancer: Lyon; 1984.
5. Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral

submucous fibrosis over a 17-year period. *Community Dentist Oral Epidemiol.* 1985; 13(6):340-1.

6. Gupta PC, Sinor PN, Bhonsle RB, Pawar VS, Mehta HC. Oral submucous fibrosis in India: A new epidemic? *Nat Med J India.* 1998; 11(3):113-6.

7. Gupta PC. Mouth cancer in India: A new epidemic? *J Indian Med Assoc.* 1999; 97(9):370-3.

8. Bhattacharjee A, Chakraborty A, Purkaystha P. Prevalence of head and neck cancers in the north east an institutional study. *Indian Journal of Otolaryngology and Head and Neck Surgery.* January-March 2006; 58(1):15-19.

9. Changrani J, Gany FM, Cruz G, Ross Kerr, Ralph Katz. Pan and Gutkha use in the United States: A pilot study in Bangladeshi and Indian-Gujrati immigrants in New York City. *J Immigr Refug Stud.* 2006; 4(1):99-110.

10. Pickwell SM, Schimelpfening S, Palinkas LA. "Betelmania". Betel quid chewing by Cambodian women in the United States and its potential health effects. *West J Med.* 1994; 160(4): 326-30.

11. Chaturvedi P. Gutkha or areca nut Chewer's syndrome. *Indian J Cancer.* 2009; 46(2):170-2.

12. Nitin J, Nagaraj K, Shashidhar Kotian M. Arecanut and tobacco use among school children in a village in South India – A cross-sectional study. *AMJ.* 2010; 3(5):299-303.

13. Gunaseelan Rajan, Sowmya Ramesh, Shanthi Sankaralingam. Arecanut use in rural Tamil Nadu: A growing threat. *Indian J Med Sci.* 2007; 61(6):332-7.

14. Prabha S Chandra, Uzma Mulla. Arecanut: The hidden Indian 'gateway' to future tobacco use and oral cancers among youth. *Indian J Med Sci.* 2007; 61(6):319-21.

15. Singh V, Pal HR, Mehta M, Kapil U. Tobacco consumption and awareness of their health hazards amongst lower income group school children in national capital territory of Delhi. *Indian Pediatr.* 2007; 44(4):293-5.

16. Nair U, Bartsch H, Nair J. Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. *Mutagenesis.* 2004; 19(4):251-62.

17. Nair J, Ohshima H, Friesen M, Croisy A, Bhide SV, Bartsch H. Tobacco-specific and betel nut-specific N-nitroso compounds: occurrence in saliva and urine of betel quid chewers and formation in vitro by nitrosation of betel quid. *Carcinogenesis.* 1985; 6(2): 295-303.

18. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Betel-quid and areca-nut

chewing and some areca-nut derived nitrosamines. *IARC Monogr Eval Carcinog Risks Hum.* 2004; 85:1–334.

19. Sharan RN. Association of betel nut with carcinogenesis. *The Cancer Journal.* 1996; 9:13-19.

20. Gupta PC, Warnakulasuriya S. Global epidemiology of Arecanut use. *Areca nut symposium. Addict Biol.* 2002; 7:77-83.

21. Chaturvedi P. Areca Nut or Betel Nut Control is Mandatory if India Wants to Reduce the Burden of Cancer Especially Cancer. *International Journal of Head and Neck Surgery.* 2010; 1(1):17-20.

22. Tzuo-Yun Lan, Wen-Chiung Chang, Yih- Jian Tsai, Yi-Li Chuang, Hui-Sheng Lin, Tong-Yuan Tai. Areca Nut Chewing and Mortality in an Elderly Cohort Study. *Am J Epidemiol.* 2007; 165(6): 677–83.

23. Deng JF, Ger J, Tsai WJ. Acute toxicities of betel nut: Rare by probably overlooked events. *Clinical Toxicology.* 2001; 39(4):355-60.

24. Chiang WT, Yang CC, Deng JF, Bullard M. Cardiac arrhythmia and betel nut chewing—Is there a causal effect? *Vet-Hum-Toxicol.* 1998; 40(5):287-9.

25. Chen TH, Chiu YH, Boucher BJ. Transgenerational effects of betel-quid chewing on the development of the metabolic syndrome in the Keelung community-based integrated screening program. *Am J Clin Nutr.* 2006; 83(3):688-92.

26. Benjamin AL. Community screening for diabetes in the National Capital District, Papua New Guinea: Is betel nut chewing a risk factor for diabetes? *Papua New Guinea Medical J.* 2001; 44(3-4):101-7.

27. Tung TH, Chiu YH, Chen LS, Wu HM, Boucher BJ, Chen TH. A population-based study of the association between Areca-nut chewing and Type 2 diabetes mellitus in men. *Diabetologia.* 2004; 47(10): 1776-81.

28. Taylor RF, al-Jarad N, John LM, Conroy DM, Barnes NC. Betel-nut chewing and asthma. *Lancet.* 1992; 9;339(8802): 1134-6.

29. Yang MJ, Chung TC, Hsu TY, Ko YC. Betel quid chewing and risk of adverse birth outcomes among aborigines in eastern Taiwan. *J Toxicol Environ Health A.* 2001; 64(6): 465-72.

30. Lopez-Vilchez MA, Seidel V, Farre M. Areca-nut abuse and neonatal withdrawal syndrome. *Pediatrics.* 2006; 117(1): e129-31.

31. Jeng JH, Chang MC, Hahn LJ. Role of areca nut in betel quid-associated chemical carcinogenesis: current awareness and future perspectives. *Oral Oncol.* 2001; 37(6):477-92.