NATIONAL CENTRE FOR DISEASE INFORMATICS AND RESEARCH
NATIONAL CANCER REGISTRY PROGRAMME
Indian Council of Medical Research

Map showing network of centres that are transmitting data

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Areca Nut use and Oral cancer and pre cancer in India
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Increasing Incidence of Mouth Cancer: A recent report of the National Cancer Registry Program in India showed that highly significant increases in incidence rates of mouth cancer in men had occurred in several population based cancer registries during the period of data availability up to 2010 [NCDIR-NCRP, 2013]: Bhopal, Mumbai, Delhi, Dibrugarh and Ahmedabad (Rural) (Table 1). In addition, a recent analysis of mouth cancer data from the Ahmedabad urban population based registry also found a steep increase in mouth cancer incidence in men from 1995 to 2010; there, incidence rates age standardised and adjusted to world population increased from 9.6 in 1985 to 25.4 in 2010 with the increase being steeper in younger age groups [Gupta et al., 2014].

Table 1: Mouth cancer incidence in men in two time periods in selected old and new population based cancer registries in India.

<table>
<thead>
<tr>
<th>Registry</th>
<th>Year 1</th>
<th>Incidence Rate</th>
<th>Year 2</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhopal, Madhya Pradesh</td>
<td>1988</td>
<td>5.9</td>
<td>2010</td>
<td>11.2</td>
</tr>
<tr>
<td>Delhi</td>
<td>1988</td>
<td>3.0</td>
<td>2010</td>
<td>7.1</td>
</tr>
<tr>
<td>Mumbai, Maharashtra</td>
<td>1998</td>
<td>5.5</td>
<td>2010</td>
<td>8.3</td>
</tr>
<tr>
<td>Ahmedabad Rural, Gujarat</td>
<td>2004</td>
<td>6.5</td>
<td>2010</td>
<td>12.7</td>
</tr>
<tr>
<td>Dibrugarh, Assam, Assam</td>
<td>2003</td>
<td>5.7</td>
<td>2010</td>
<td>10.2</td>
</tr>
</tbody>
</table>

Association with Areca Nut Consumption: All these registries showing increases in mouth cancer incidence in men are located in states with a high prevalence of consumption of tobacco products containing areca nut, mostly gutka and mawa according to the report of the Global Adults Tobacco Survey [IIPS &
MOHFW, 2010]. Areca nut consumption has nearly doubled in India during 1991-2001 to 2009-10, from 2.5 to 5.2 lakh tons and is growing about 5% each year [Kammardi et al., 2012], owing to intense marketing efforts of the industries manufacturing packaged products.

The traditional way of consuming areca nut in India was with betel leaf (called betel quid or pan) and tobacco began to be added since its introduction in India by the Portuguese in the 1600s [Reddy and Gupta, 2004]. Areca nut consumption today is mostly in dry flavoured packaged form (pan masala, gutka, mawa, kharra) and has become the most common way of consuming areca nut since the mid-1970s. In 2010 in India, these were used by 13.1% of men and 2.9% of women, while betel quid was used by 7.5% of men and 4.9% of women in India as a whole. Areca nut products are typically chewed and then held just inside the cheek (buccal mucosa). Oral submucous fibrosis is typically found in the buccal mucosa area adjacent to where the areca nut quid is generally held.

Consumed with or without betel leaf, areca nut is most commonly consumed with tobacco, a known human carcinogen. While use of betel quid with tobacco has been linked with oral cancer in the medical literature for nearly a century, the added tobacco has been viewed as the main culprit [IARC, 2004]. In the past decade or more, mouth cancer has been diagnosed with increasing frequency in users <35 years of age who mainly use packaged areca nut [Chaudhry, 1999, Gupta, 1999]. This has brought the potential carcinogenicity of areca nut under the scanner. A thorough review of epidemiological studies on areca nut and cancer and experiments in animals by the International Agency for Research on Cancer published in 2004 concluded that areca nut by itself is a carcinogen to humans, as it has been linked with oral cancer [IARC, 2004]. The direct relationship of areca nut use with oral pre-cancer is even more remarkable.

**Oral Pre-cancers:** Four case control studies are available on oral submucous fibrosis (OSF) that provides odds ratios for different areca nut products. These studies were based in Gujarat [Sihor et al., 1990], Kerala (Jacob et al., 2004), Karnataka [Bathi et al., 2009] and Uttar Pradesh [Mehrotra et al., 2013]. All four studies showed significantly elevated odds ratios for OSF for areca nut use in its various forms. The most interesting finding of these studies was that users of areca nut without betel leaf, as in mawa, pan masala or gutka had much higher ORs than those who used betel quid in three studies [Sihor et al., 1990; Bathi et al., 2009; Mehrotra et al., 2013].

In the study from Uttar Pradesh, a significant dose response relationship for frequency of use per day for betel quid with tobacco was found for categories 1-6 and >6 times per day whereas for pan masala, categories were 1-2 and > 2 times used per day [Mehrotra et al., 2013]. In an earlier case series study of OSF patients in Hyderabad, pan masala and or gutka chewers presented with OSF just after 2-3 years whereas betel quid chewers developed OSF after 6-10 years. This study concluded that chewing of pan masala and or gutka can cause OSF faster than betel quid due to the absence of betel leaf and the higher consumption by weight of areca nut [Babu et al., 1996].

Leukoplakia has also been found associated with areca nut use. A case control study from Kerala [Jacob et al., 2004], reported an odds ratio of 4.0 for leukoplakia for chewers of pan without tobacco and an odds ratio of 12.8 (95% CI: 1.6-101.2) for chewers of areca nut by itself (which may include lime). The trends for both frequency and duration were significant (p<0.0001). An intervention study also in Kerala, aimed at reducing tobacco consumption (mainly as betel quid with tobacco), showed a substantial reduction in leukoplakia incidence among chewers after 5 years (by around 50% in men and over 25% in women), compared to the non-intervention
group [Gupta et al., 1986]. The reduction strengthened further after 10 years, the intervention to control incidence ratio being 0.63 among men and 0.45 among women chewers [Gupta et al., 1992].

**Oral Cancer**: Eight recent case control studies on oral cancer showed significantly elevated odds ratios for oral cancer for betel quid chewers with tobacco, regardless of gender. One study was conducted in Madhya Pradesh [Dikshit and Kanhere, 2000], two were in Maharashtra [Jussawala and Deshpande, 1971; Wasnik et al., 1998], and the rest, in South Indian States - Karnataka, Kerala, and Tamil Nadu [Nandakumar et al., 1990; Balaram et al., 2002, Znaor et al., 2003; Muwonge et al., 2008; Mahapatra et al., 2015]. Six of these studies showed elevated odds ratios for chewing of betel quid without tobacco as well, significant in the four largest studies. The odds ratios for betel quid with tobacco tended to be higher than those for betel quid without tobacco and odds ratios were higher for women than for men. One study in Kerala also reported an elevated and significant odds ratio for women who chewed areca nut without tobacco [Muwonge et al., 2008].

In a cohort study in Karunagapally, Kerala, incidence of oral cancer among 144,417 individuals aged 30-80 years (women 54%), followed up between first interview during 1990-7 and until the end of 2005, significantly elevated relative risks were found for the use of betel quid, mainly with tobacco: for women 5.5 (95% CI: 3.3 - 9.0) and for men 2.4 (95% CI: 1.7 - 3.3) [Jayalekshmi et al., 2009; Jayalekshmi et al., 2011].

In a cohort study on cancer mortality in Trivandrum, Kerala with 164,072 rural participants aged 34 years and above (60.2% women) followed up between 1996 and 2005 for a mean duration of 6.5 years, chewers without tobacco (generally betel quid) had an adjusted hazard ratio of 1.47 (95% CI: 0.98 - 2.19)) for death due to tobacco-related cancers including oral cancer; those who chewed with tobacco had a hazard ratio of 1.27 (95% CI: 1.07 - 1.52) [Ramadas et al., 2010].

The Mumbai Cohort Study on mortality that analysed for oral cancer among urban users of areca nut containing substances has had relative risks that were elevated but not significant [Gupta et al., 2005; Pednekar et al., 2011]. In another analysis of incidence of cancer among 87,222 men aged 35 years and older, after an average 7.4 years of follow-up the relative risk for oral cancer for smokeless tobacco use combined was significant (RR 1.48, 95% CI: 1.03 - 2.13) [Pednekar, 2011].

**Conclusion**: In view of the clear elevated risk for oral cancer posed by the use of areca nut and its products, their control, such as through bans, is justified to contain the adverse effects of this substance on the population and improve public health.

**References**


22. Pednekar MS, Gupta PC, Yeole BB, Hebert JR. Association of Tobacco Habits, including Bidi Smoking, with Overall and Site-Specific Cancer Incidence: Results from the Mumbai Cohort Study. Cancer Causes and Control. 2011; 22(6), 859-68.


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Methods for Appreciation of Risk Levels

- A statistically significant excess risk among habitués,
  - Case Control studies, Retrospective studies, Cohort studies
  - Odd's Ratio, Relative Risk, Hazard Ratio, Attributable Risk
- A dose effect relationship
- Withdrawal reducing the risk
- Similar results from various population groups & over time
- Biological Plausibility Including Laboratory Evidence.
- Clear Definitions of Study factors essential