Betel Quid Addiction: Blessing or Curse, A Study of North East Population of India

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Abstract
Introduction: Oral cancer is most common cancer in males and third most common in females, one of the main causative agent being use of chewing betel quid (BQ). Areca nut (Areca catechu), a major component of BQ, contains certain alkaloids that give rise to nitrosamines. CYP2A6 genetic polymorphism were studied among the Eastern and North eastern indian population.

Methods: In this present study subjects were screened from Department of E.N.T. & Oral and Maxillofacial surgery of RKMSP hospital, Kolkata and different areas of Eastern and North Eastern states of India. Polymorphism of CYP2A6 gene was studied from EDTA blood.

Results: Some of the cases had more than one addiction. It has been found that most of the subjects had betel quid chewing habit. Early metabolizer are susceptible to oral cancer where as in case of poor metabolizers chances are less.

Conclusion: Betel quid has an immense role in changing the oral pathology and developing oral cancer.

Keywords: Oral cancer; Betel quid; CYP2A6 polymorphism

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Introduction

Cancer never kills but delay always. It is a true saying. The North East region especially Assam and Meghalaya is turning to be the stock house of Oral cancer due to many reasons. The oral cancer is said to be easily detectable and treatable but still the patients in north east come to know of it at the final or last stage. Any type of cancer which occurs in some internal organs, requires several investigations to be diagnosed, but to detect any sort of cancerous formation in the oral cavity, a person requires a mirror and the sunlight. It clearly means that the people in North East India are still not properly aware of the disease so called-Cancer. As like the other cancers, oral cancer can be healed only at the earlier stages when it does not spread. Oral cancer means abnormal growth or ulcer inside the oral cavity. The oral cancer is a subtype of Head and Neck Cancer and the oral cavity includes lips, tongue, inner parts of the cheeks, floor of the mouth, gums, hard and soft palates (roof of the mouth). The most common type of oral cancer is the Squamous Cell Carcinoma, followed by Adenocarcinoma at the second place. The common symptoms are Leukoplakia (white patches) or Erythoplakia (red patches) on the soft tissue of the mouth usually painless at the initial stage. In the case of cancer on tongue, a person might develop small ulcer on the tongue in colored or dark condition that cannot be healed with general medications. Patient may feel burning sensation or pain at the advanced stages. Change in taste buds, difficulty in swallowing, uncommon sensation while taking foods or drinks are other common symptoms. Advanced stage of the ulcer or tumour may also lead to unmanageable bleeding. The tradition of chewing Betel Nut in North Eastern states of Assam and Meghalaya is very old. Most of the people in this region like to have betel nut with the betel leaf. But many of them like the combination of Slaked lime and raw tobacco along with the betel nut and leaf which is very dangerous and contributes causing highest number of oral cancers in the region. According to a British Journal 358 male and 144 females are found to be suffering from oral cancer, just due to the habit of chewing betel nut. Even the International Agency for Research on Cancer or IARC has declared the betel nut as one of the major Carcinogen, that provide aid to cancer and it has reached to the conclusion that there are sufficient evidences that chewing of betel nut leads to cancer.

Plenty of betel nut trees and betel leaf cultivations in North East India. Betel nut in other language is also known as the Areca nut. It can be availed in either fresh or dry forms. The fresh form of betel nut is greenish in colour with a soft layer inside where as the colour of the dry betel nut is brownish and hard from every side. However the fresh form of betel nut is mostly preferable in the north east region of India. In local language a fresh betel nut is known as Tamol and the dry is called as Supari. Frequent and regular scratches of betel nut forms ulcers in the oral cavity. Betel nuts are served as mouth fresheners usually wrapped in betel leaf. The betel leaf is very well known as Paan in this region of India. Just like the betel nut, the betel leaf had been also found as a cancer causing agent. Although being green in colour, the betel leaf does not contain any necessary vitamins or minerals like other green leafy vegetables. Sometime the betel leaf filled with betel nut is served with slaked lime. This lime is a chemical compound that contains inorganic substances like carbonates, oxides and hydroxides. This strong chemical compound often burns the soft tissues or mucosa in the oral cavity that form scars or ulcers. In many occasions tobacco is also filled in betel nut along with betel nut and lime. This chewable
tobacco causes irritation on the soft membranes in the oral cavity. This may alter the normal process of cell division. These tobaccos help to form free radicals that try to steal electrons from the molecules in the body. This way the free radicals affect the normal cells making them go abnormal and disabled. Combining betel nut, betel leaf, lime and tobacco together one can lead the way to oral cancer very fast. This combination is favorable in most of the places of Meghalaya [1].

Betel quid is fourth most commonly used psychoactive substance after tobacco, caffeine and alcohol worldwide. The betel (Piper betle) is the leaf of a vine belonging to the Piperaceae family, which includes pepper and kava. It is valued both as a mild stimulant. Users are easily identified due to black brown teeth and stain the tongue with oral mucosa [2,3]. Betel leaf contain large amount of carcinogens known as safrole. Betel quid (BQ) products, with or without tobacco, have been classified by the International Agency for Research on Cancer (IARC) as group I human carcinogens that are associated with an elevated risk of oral potentially malignant disorders (OPMDs) [4] and cancers of the oral cavity and pharynx. The Cytochrome P450 (CYP) families are divided into 14 gene families of which CYP1, CYP2 and CYP3 are primarily active in the metabolism of a wide range of chemicals and these CYPs families are implicated in the metabolic activation of BQ and areca nut-specific nitrosamines [5].

CYPs are located on human chromosome 19. The CYP2A6 gene consist of 350 kilobases located at 19q 12 – 19q 13.2 [6-8]. Genetic defects in the CYP2A6 gene may also effect susceptibility to pre carcinogen in the environment. People are classified as EM known as early metabolizers and PM known as poor metabolizers based on genetic variation [9]. The PM phenotype are incapable of metabolizing the exogenous compound but EM phenotype are capable of metabolizing the exogenous compound [10, 11].

Our present work based on case control study suggest that the CYP2A6 genetic polymorphism has an impact on susceptibility to oral cancer.

(A) Screening of Subjects
I) North East camp: - 56 subjects were screened at a camp held in Karimganj, Assam. Out of whom 33 were betel quid chewers.
II) a) North Eastern India camp (Silchar): - 729 subjects were screened at camps held in Maynagarh, Dudhpatil and at Silchar Ramakrishna Mission ashram. 37 cases had oral lesions.
   b) North Eastern India camp (Shillong): - 105 subjects were screened at a camp held in Shillong Ramakrishna Mission dispensary, Sohrynkham, Mawlynghat, Umphyrnai. 39 had oral lesions

(B) Methods
i) Detailed history were taken from all cases by filling up questionnaire.

ii) Molecular study
PCR of different cases were performed with forward and reverse primer for case and control sample at 58° C for annealing temp. with 35 cycle and total amount of PCR product is 26.5µL.
Results

Table 1 Detailed history of subjects of different areas

<table>
<thead>
<tr>
<th>PLACE</th>
<th>NO</th>
<th>AGE GROUP (in years)</th>
<th>Addiction</th>
<th>Tea Drinker</th>
<th>Non Tea Drinker</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORTH EAST CAMP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Assam, Karimganj</td>
<td>56</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31-40</td>
<td>41-50</td>
<td>51-60</td>
<td>61-70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>9</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td>40</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>2. Silchar, Assam</td>
<td>37</td>
<td>5</td>
<td>10</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>2</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>3</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Shillong, Meghalaya</td>
<td>39</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>2</td>
<td>9</td>
<td>28</td>
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<td></td>
<td></td>
<td>36</td>
<td>3</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>132</td>
<td>20</td>
<td>20</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>10</td>
<td>30</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>103</td>
<td>29</td>
<td>109</td>
<td>23</td>
</tr>
</tbody>
</table>

Note: Some cases had more than one addiction. More than 75% cases had betel quid chewing habit.

Table 2 Poor metabolizer and Early metabolizer of different area

<table>
<thead>
<tr>
<th>Area</th>
<th>No of betel quid chewers</th>
<th>Poor Metabolizer (PM)</th>
<th>Early Metabolizer (EM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karimganj, Assam</td>
<td>33</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Silchar and Shillong</td>
<td>103</td>
<td>33%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Note: Early metabolizers are susceptible to oral cancer whereas in case of poor metabolizers chances are less. In Silchar and Shillong area more than 50% are early metabolizers.

Discussion

Oral cancer is one of the leading cancers in most Asian countries. India has largest betel quid consuming population in the world. The habit of chewing betel quid is due to low cost, easily available and also as a mood elevator in the day to day busy scheduled life. CYP2A6 gene deletion reduces oral cancer risk in betel quid chewers in Sri Lanka. Poor metabolizer are less prone to oral cancer than early metabolizer due to CYP2A6 gene polymorphism. Subjects who have polymorphism in CYP2A6 are poor metabolizer and showed band in PCR. Early metabolizer had normal CYP2A6 gene and
showed no band in PCR.

**Conclusion**

The substances which are present in the betel quid not only have the cytotoxic, mutagenic property but it also involved in genetic, enzymatically and molecular mechanism in the development of carcinogenesis. In our study it has been found that more than 50% cases from North Eastern states were poor metabolizer, whereas more than 50% cases of Eastern region (except North 24 Pgs) were early metabolizer.

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**References**