

# Areca Nut and its Products: A Culprit for Many Cancers

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## ABSTRACT

This article is to give a comprehensive review about the areca nut, different products made from it, and the important cancers associated with the use of different products of areca nut. Areca nut is a chewing substance consumed by a large population around the globe including our country Pakistan. Areca nut is a constituent of many products like supari, pan, gutkha and mawa, which are frequently used in Pakistan especially in urban areas. Areca nut is very dangerous for human health as it is associated with a large number of benign and malignant diseases. Different products of the areca nut are associated with very common cancers like mouth cancer, cancer of oesophagus, salivary gland cancer, hepatocellular cancer and different other head and neck cancer. To answer the research question "Areca nut and its products: A Culprit for many cancers" the literature review was done using Pubmed, google scholar and Medline using keywords "areca nut, paan, gutkha and cancers" and relevant articles from the year 2000 to the year 2020 were searched and relevant articles were selected in this review. The cancers of the oral cavity, oesophagus and liver develop in habitual chewers of areca nut due to the presence of some dangerous chemicals present in areca nut like arecoline which is an alkaloid. Arecoline and some other alkaloids cause cancer of the human body by inhibiting the tumor suppressor gene. Areca nut and its products should be strictly banned in Pakistan to decrease the burden of these cancers.

**Keywords:** *Areca nut, gutkha, paan, cancers, chewing products.*

## INTRODUCTION

Areca nut which is also called betel nut is the seed obtained from the oriental palm tree *Areca catechu*. It is the basic part of a variety of widely used chewing products. The areca nut is cut into thin slices, either in natural or processed form, may be mixed with a wide variety of substances [1]. Areca nut is a chewing substance used from very old times as documented in the literature. Its use was documented in Indopak in periods from 300 to 750 AD. It is trusted that the nut was transferred to Europe by Marco Polo nearby in 1300 AD. The word 'Areca' is gotten from the Malaysian word *adakka* which means areca nut [2]. The Palm tree of the areca nut is shown in **Fig. (1)** [3].

## OBJECTIVE

To formulate a thorough review article on the association of cancer and areca nut and its products.

Rationale: To aware the researchers of the cancer-producing effects of areca nut and its products.

## MATERIAL AND METHODS

We searched the published literature using keywords areca nut, gutkha, paan, cancers, by using search engines PubMed, Medline and Google scholar. A total of 156 related articles were initially selected. The research

articles published from the year 2000 to the year 2020 were included in the study, the rest were excluded, after studying the initial 156 papers, finally 40 were included in this review.

## PREVALENCE OF ARECA NUT AND ITS DIFFERENT PRODUCTS

It is estimated that Areca nuts in different forms are chewed by around 600 million people worldwide. The rough estimation is that 10± 20% of the world's people use areca nuts or their products [4]. Areca nut and its different commercial products are used by numerous nations like India, Pakistan, Sri Lanka, Thailand, Bangladesh, Malaysia, New Guiana, Cambodia, China and Indonesia [5]. India is the greatest maker and also the purchaser of areca nut, a survey was conducted in Wardha an Indian city, that survey found that gutkha using frequency was 20% in women and 46.4% in males [6].

Pakistan stands second next to India in which these areca nut items are expended, with a frequency of male Pakistani using areca 21.3% and females 19.3%. In Pakistani largest city, Karachi 40% of the residents were daily users of areca nut products [7]. The prevalence of areca nut in the form of gutkha and paan has been reliably seen in specific populations with different frequencies. A study conducted on residents of Karachi previously found that 46% of people consumed gutkha on daily basis. Similarly, in another study, its prevalence was seen at 35% among the patients visiting a health care center in Karachi [8].

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Areca nut which is also called betel nut is used as a chewing substance in different forms like supari, pan or betel quid, main puri, and gutkha [7].

### DIFFERENT PRODUCTS OF ARECA NUT USED IN PAKISTAN

The different preparations of areca are shown in **Fig. (2)**.

#### Sweet Supari

When small and roasted pieces of areca nut, is often served to guests after meals, when saccharin as sweetener, menthol and the artificial flavor is added called as Sweet supari [9].

#### Pan

The areca nut wrapped in betel leaf added with catechu, lime, and sometimes crushed tobacco. Different additional things like flavors, sugars, cardamom, saffron, cloves, aniseed and turmeric when added in different localities are called as Pan or Betel quid [10].

#### Gutkha

Gutkha is a dry, generally marketable product of areca nut that contains lime, catechu, condiments and tobacco in powdered form, that are combined with different flavorings and sometimes sugars are added and packed in sachets [11].

#### Mawa

The mixture of areca nut pieces or shavings, watery slaked lime, dried crushed tobacco leaf and catechu [12].

#### Pan Masala

When the areca nut is cut to pieces, and slaked lime, cardamom, cinnamon, fennel seeds, menthol, and sweet & aromatic flavorings are added. It may or may not contain tobacco [13].

### ARECA NUT PRODUCTS AND CANCER

The leading cause of death among developed nations is cancer. Cancer stands as the second important reason in terms of mortality in poor countries [14]. There is a huge burden of cancer in developing nations and it is increasing due to multiple factors like increasing population, aging, increase in the risk factors associated with cancers like sedentary lifestyle, physical inactivity, smoking, and other hazards [15]. The International Agency for Research on Cancer and World Health Organization classified the areca nut as a Group 1 human carcinogen. There are important and reliable pieces of evidence are present which show that areca nut increases the risk of sufficient evidence of different cancers like esophagus, oral cavity, pharynx, and different precancerous oral lesions like submucous fibrosis [16].

#### Oral Cancer

Cancer of the oral cavity is a common health problem globally as it is hugely associated with morbidity and mortality. The relevance of epidemiological knowledge

in oral cancer is mainly based upon the fact that 5-year survival rates have been reported to be about 50% [17, 18]. The main culprit in cancer of the oral cavity is that it is mostly diagnosed at the 3<sup>rd</sup> advanced stage particularly in underdeveloped countries [19]. The increased risk for the development of mouth cancer is reported in areca nut users in many studies. The Taiwanese people use areca nut in form of quid (pan) frequently. The relative risk was calculated for oral cancer among them was found as 58.4 which is very significant (95% confidence interval 7.6 to 447.6) [20]. Oral cancer due to areca nut products use is shown in **Fig. (3)** [21].

Oral cancer includes a malignant tumor of the mouth, lip or tongue. It is generally a malignancy of squamous cell type. In the treatment of oral cancers many functional and cosmetic defects accompany. The prognosis is also poor. The leukoplakia which is a whitish lesion or the reddish lesion called erythroplakia develops in people chewing paan as an early sign of damage to the oral mucosa. In paan users, oral submucous fibrosis also develops, which is stiffness in the mucosa of the mouth and oral cavity. All these well-known pre-tumor conditions are easily diagnosed and are an important predictor of the risk of oral cancer. These lesions are reported to turn into a malignancy over several years in around 2–12% of individuals. The malignant change of non-homogeneous lesions involving erythroplakia and nodular leukoplakia is particularly high depending on the time and is reported to be in the range from 15 to 40%. Almost every paan chewing-related oral cancer is first seen as a clear premalignant stage at the site of cancer development. Oral Submucous Fibrosis is mainly caused by the consumption of betel nut and its different products [8].

In Pakistan, a study was done to clarify the independent association between oral cancer and chewing paan. In this study primary cases of oral squamous cell carcinoma, from 3 tertiary care hospitals in Karachi were taken, these were confirmed cases of cancers on Biopsy. These were compared with controls similar for age, gender, hospital and time of occurrence, the persons with a past or present history of any malignant tumors were excluded from the study. There were 79 cases and 149 controls from 3 different hospitals Aga Khan Hospital Karachi, Abbasi Shaheed Hospital, and Civil Hospital Karachi, the result of the study showed a positive association of carcinoma with paan or betel quid usage [22].

In Southern India, in the cities of Madras, Bangalore and Trivandrum a case-control study was done in which 591 cases of oral cavity cancer were selected, among them 282 were women, and 582 controls from the hospital were taken in which 290 were women, frequency-matched with cases by age and gender. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from unconditional multiple logistic regressions and adjusted for age, gender, center, education, chewing

habit were assessed and concluded that Paan chewing is an important reason of oral cancer in them most particularly, in women [23].

### Cancer of Oesophagus

Cancer of oesophagus is the 9<sup>th</sup> most commonly occurring malignant tumor and the 6<sup>th</sup> common cause of death due to cancer worldwide. Oesophageal cancer is shown in **Fig. (4)** [24]. Similarly in another study betel nut chewing as a suspected risk factor for oesophageal cancer in Assam, India was studied and strong relation was found between chewing betel nut or its products and cancer of oesophagus [25]. Another important study of Taiwan has shown that chewing areca nut plays an important role in the development of squamous cell carcinoma of the esophagus [26]. Similarly in a meta-analysis, it was seen that Areca nut chewing is independently associated with an increased risk of malignancy of esophagus of squamous-cell type in Asians [27].

The subepithelial fibrosis was seen more frequently in consumers of areca nut in form of gutka, pan masala for more than 5 years than those persons who consume these chewing products for a limited duration [28].

Another case-control study was done in Taiwan to check the relation between betel nut chewing and oesophageal cancer. In that 277 controls and 104 cases of malignant squamous-cell carcinoma of oesophagus were selected and found that subjects who chewed betel nut from 1 to 495 betel-year and more than 495 betel-years (about 20 betel quid per day for 20 years) had 3.6-fold (95% CI = 1.3–10.1) and 9.2-fold risk (95% CI = 1.8–46.7), respectively, in causing cancer of oesophagus in comparison to non-chewer of betel nut [29].

In the same way, another case-control study was conducted in Taiwan in multiple centers to clarify the additive effects of tobacco in form of smoking, paan chewing and alcohol intake, on the risk of cancer of oesophagus. In this study, 513 diagnosed cases of cancer of squamous cell carcinoma of the esophagus on biopsy were enrolled and matched with 818 control subjects of the same age and gender. There was a significant dose-response relationship between the duration and intensity of using these products and the cancer development in the oesophagus among cases in comparison to controls [30].

### Hepatocellular Cancer

The cancer of the liver called Hepatocellular Carcinoma is one of the most common cancer globally: it ranks as the 5<sup>th</sup> most frequent cause of cancer in males and the 7<sup>th</sup> one among women, in men the approximate new cases were 520,000 and in women 230,000 in 2008 [31]. Although Hepatocellular Carcinoma is a life-threatening disease for which treatment is yet not satisfactory, there is sufficient preventive knowledge of this tumor [32]. The risk of liver carcinoma is also seen in persons eating areca nut in the form of paan. In a case-control research

study in which 263 patients and healthy controls were compared and it was concluded that habitual paan usage is an independent risk factor for HCC. The risk of carcinogenesis increase with frequency, amount and duration of areca nut use [33].

Habitual paan usage and risk for liver Carcinoma complicating Cirrhosis was assessed in a case-control study. Subjects enrolled included 210 pairs of sex- and age-matched patients of cirrhosis complicated with HCC matched with healthy controls. The conclusion was made that betel quid chewing is an independent risk factor for cirrhotic liver cancer [34]. Similarly, the risk of liver cancer and habits of paan chewing, alcohol intake, and smoking were studied in Taiwan in a cohort of 2416 HBsAg-seropositive and 9421 HBsAg-seronegative male residents and concluded that Areca nut in the form of Betal quid means paan is associated with Hepatocellular carcinoma [35].

### Salivary Gland Cancers

Cancers of Salivary gland are also common head and neck cancers. Among the tumors of the salivary gland 64%–80% originate in the parotid glands, and among parotid tumors 15%–32% are malignant. The submandibular gland tumors are found at 7% and 11%, among them 41%–45% being malignant. The sublingual gland tumors are only less than 1% but interestingly the majority of these are malignant [36].

Betel nut chewing is also associated with Salivary gland tumors the relationship was seen in a case-control study, in which 1845 patients from 35–65 years of age were selected, among them 239 patients were with pathologically proven Salivary gland tumors, these were compared with 1606 controls from the health clinics and found a positive correlation between betel nut chewing and SGT [37].

## PATHOGENESIS OF CANCER DUE TO ARECA NUT

The cancer-producing property of the areca nut is due to certain alkaloids present in it. The major alkaloids are Arecoline, arecaidine, and guvacine. These alkaloids are the primary cause of the pathogenicity of cancer due to areca. Arecoline is the major alkaloid present in the areca nut. These alkaloids including Arecoline when chewed in the body are converted to nitroso-derivatives, one mechanism of tumor production is that this nitro compound induces oral mucosal lesion. Another way is by altering the autophagy process. The mechanism behind this is that Areca nut constituent alkaloids are captured by oral cells. There is clathrin-mediated endocytosis to start an autophagy sequence. The other way is when oral cancer cells are treated with areca nut extracts multiple mechanisms operate like autophagosome formation, Beclin-1 or Atg5 accumulation and LC3-II transition [38].

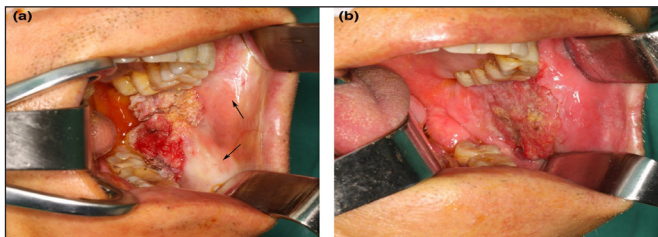
When the areca nut is chewed and its alkaloids enter the acidic environment of the stomach the Nitrosamines



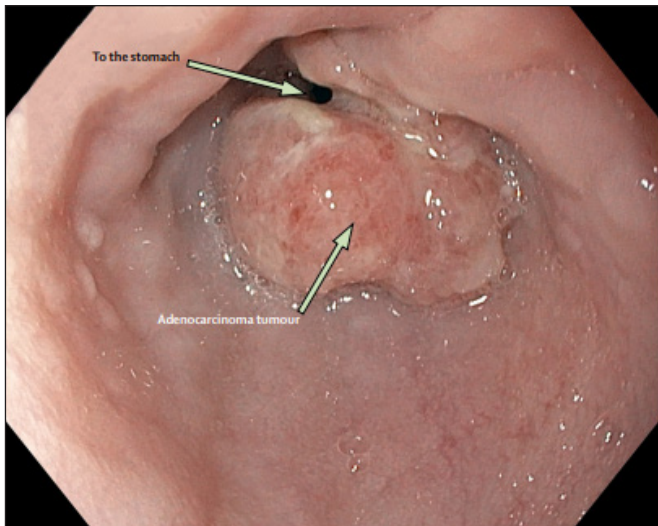
**Fig. (1):** Areca palm tree with fruit and branches [3].



**Fig. (2):** Different products of areca nut available in the market [12].



**Fig. (3):** Mouth Cancer due to areca nut chewing [21].



**Fig. (4):** Endoscopic photograph of carcinoma oesophagus obstructing the distal Oesophagus [24].

are produced by nitrosation of the alkaloids in the presence of nitric oxide generated by bacteria. Two of these Nitrosamines derivatives have been found to be

cancer-causing in different studies seen especially in animals, among these Nitrosamines most important is methylnitrosamino propionitrile [39].

It has also been proposed that areca nut alkaloids especially Arecoline produce cancer by the mechanism of expressing cell cycle checkpoint suppressors which include p21, p27, p53, and Ches1. Due to these changes cell cycle occurs with defective DNA replication [40]. In summary, the areca nut alkaloids cause cancer by autophagy formation and by inhibition of tumor suppressor genes.

### CONCLUSION

It is concluded from this review that areca nut and its products are widely used in the Pakistani community. These are very dangerous for our health as they are responsible for a wide variety of cancers like mouth, salivary gland, oesophagus and liver.

### RECOMMENDATIONS

It is recommended that areca nut and all products like pan gutkha and mawa should be strictly banned to save our community from the burden of cancer.

### LIMITATION OF STUDY

No limitation of the study.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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