The relationship between betel nut chewing and the development of carcinogenic lesions: A narrative review

Arnith Eechampati[1], Nicole Steel[2], Bhuvaneshwari Muchandi[2], Trisha Patil[3], Arun Arumugam[3], Donny Delp[1]

AFFILIATION
1 Philadelphia College of Osteopathic Medicine–Georgia Campus, Suwanee, United States
2 Mercer University School of Medicine, Mercer University, Macon, United States
3 Medical College of Georgia, Office of Academic Affairs, Augusta University, Augusta, United States

CORRESPONDENCE TO
Trisha Patil. Medical College of Georgia, Office of Academic Affairs, Augusta University, Augusta, Georgia, 30912, United States
E-mail: Trpatil@augusta.edu

KEYWORDS
oral cancer, betel nut, South Asia, betel nut cancer, betel nut chewing

Received: 7 January 2026, **Revised:** 27 April 2026, **Accepted:** 10 August 2026
Public Health Toxicol 2026;6(3):10
https://doi.org/10.18332/pht/230980

ABSTRACT

Worldwide, betel nut chewing is a long-standing social and cultural practice in South Asia, the Pacific Islands and many immigrant communities. Despite this societal and cultural significance, betel nut consumption is strongly linked to many negative health outcomes, predominantly oropharyngeal malignancies. This narrative review was conducted to examine the community-level implications, epidemiological evidence, biological mechanisms, and public health significance of betel nut-related carcinogenesis. Betel nut chewing is associated with a well-documented, dose-dependent risk of oral squamous cell carcinoma and other oral potentially malignant disorders, with risk increasing substantially when tobacco is used concurrently. This carcinogenic process is driven by multiple converging mechanisms: arecoline and its metabolites induce direct DNA damage and oxidative stress, while chronic exposure promotes inflammation and epithelial-mesenchymal transition, a process by which oral epithelial cells lose their normal structural characteristics and acquire invasive potential. Concurrent alcohol and tobacco use does not merely add to this risk but appears to act synergistically, and variation in DNA repair capacity may help explain why only a subset of chewers ultimately develop malignancy. The disease burden is unevenly distributed, falling disproportionately on populations in South and Southeast Asia, the Pacific Islands, and immigrant communities in Western countries, where limited awareness and restricted access to screening contribute to delayed diagnosis. Betel nut associated malignancies are a severely under-represented and under-recognized area of public health concern. To prevent cancer risk, more regulatory oversight and targeted research is necessary, which can help address gaps in public health awareness.

INTRODUCTION

Many cultures and countries throughout Asia consume betel nuts for cultural and recreational use[1,2]. The betel nut is a type of seed that is chewed for its psychoactive and stimulating properties[1,3]. While its use has a long tradition for many cultures, most partakers start chewing betel nuts early in life and continue for various reasons ranging from cultural, religious, and social[2,3]. Many South Asian and Pacific Islander communities normalize chewing betel nut for perceived health benefits[1,3].

In many regions, betel nut use is deeply embedded in cultural and religious practices. In India, Nepal, and Sri Lanka, betel nuts are offered to deities during religious ceremonies, which establish their cultural purpose as sanctified. These countries also utilize betel nuts in other sacred ceremonies such as weddings. In Malaysia, betel nuts are chewed socially among older adults[2]. Among Micronesia and Western Pacific communities, the social

nature of betel nut use is further reinforced as groups partake communally and often describe the experience as calming and energizing[1]. In addition, many immigrants to the United States, particularly from India, Bangladesh, Pakistan, Sri Lanka, and the Pacific Islands, especially Chamorro and Palauan communities, chew betel nuts to retain their cultural identity after immigration[4].

Despite its longstanding cultural significance, the nut's compounds lead to a host of concerning medical conditions, including oral disease, malignancy, and cardiovascular and metabolic effects[5-8]. Of note, the prevalence of oral cancer is elevated and has been strongly associated with continued betel nut chewing in countries across Asia[9,10].

The prevalence of betel nut use remains highest in Asia. The countries with the highest reported usage include India, Taiwan, Myanmar, and Sri Lanka[2,11]. Despite being a cornerstone of these countries' cultures, health officials have begun to recognize the significant cancer risk. However, despite ongoing health initiatives to mitigate continued betel nut use, use is still pervasive among lower income and rural communities[2]. In particular, use among adolescents and women is still emerging[2]. Among the countries with the highest prevalence of use, a low socioeconomic status stands as a common factor[2,4]. In Taiwan, demographics for the highest use within Yunlin County included males aged 40–64 years of low level of education and income[11]. This trend is further reflected in Guam, where adolescents in poorer and less educated households were more likely to chew betel nuts[4]. In addition to residents of low socioeconomic status, adolescent use is concurrently high in countries with the greatest prevalence[2,4]. In Guam, 13.5% of middle schoolers had tried betel nut[4]. Similarly, in Taiwan, 53.6% of students residing in Changhua County had tried betel nut with their families[11].

This narrative review synthesizes current epidemiological evidence and biological mechanisms underlying betel nut-associated carcinogenesis.

DEVELOPMENTS

Chemical composition and mechanism of action

To fully grasp the detrimental effects of betel nut use, an examination of its biochemical make up is required. A particular component of interest is the presence of alkaloids which are the chemical compounds that are primarily responsible for the carcinogenic effects of betel nuts. Of the alkaloids, arecoline is the most abundant biologically active within the nut. Arecoline is known to work as a muscarinic receptor agonist that leads to several cholinergic symptoms such as hypersalivation[12]. But when arecoline is metabolized into arecoline N-oxide, this becomes a pro-inflammatory agent that causes cytokine release, DNA damage, and fibroblast proliferation. The combination of these pro-inflammatory effects causes increased cellular damage that allows for increased levels of oncogenic mutations[5]. Arecoline's role as a proinflammatory agent is one of the hallmark mechanisms implicated in the formation of oral cancer. In addition to being metabolized to arecoline N-oxide by the liver, arecoline is additionally converted into arecaidine when chewed. The chewing of betel nuts and partial digestion by salivary enzymes leads to the hydrolysis of arecoline into arecaidine which induces cytokines such as TGF-B and leads to chronic fibrosis. While its specific role in malignant transformation is still being researched, researchers suspect it to be a precursor[6].

Other alkaloids present in betel nuts include guvacoline and guvacine. These are known to be minor alkaloids that function as GABA reuptake inhibitors, which contribute to increased anxiolytic effects of chewing betel nut. While not having a direct role in malignant transformation, their anxiolytic effects propagate the continued chewing which can cause further development of possible malignancies[7]. Continuing, betel nuts additionally have tannins and catechins which are known for having antioxidant properties. However, these antioxidant properties are often countered by consumption of slaked lime in betel quid, a common form of betel nut consumption, which causes the generation of reactive oxygen species and further leads to oxidative damage to both cells and DNA[7].

Beyond the compounds in betel nuts, other compounds are frequently added to enhance consumption. The primary additives included slaked lime and tobacco. As previously alluded to, slaked lime, or calcium hydroxide, is added to betel nut to increase the pH of the oral cavity. This alkaline environment improves the lipid solubility of the arecoline resulting in more systemic absorption[7]. As previously explained, the slaked lime also promotes the oxidation of polyphenols resulting in oxidative damage[5]. Tobacco is one of the primary additives in betel quid especially in regions of South Asia[6]. The nicotine within tobacco adds an addictive element to the pattern of chewing[5]. While the nicotine adds addictive potential, the nitrosamines within the tobacco are potent carcinogens which compounds the risk for oropharyngeal cancer with intrinsic carcinogenic properties of the betel nut[6]. Smaller less important additives such as masala, sweeteners, artificial flavors, and menthol are added to increase the palatability of the bitter betel nut. The addition of bright colors significantly contributes to use among adolescents[8].

Betel nuts initiate damage to host systems through a variety of different mechanisms. One of the primary effects include direct DNA damage. Arecoline and its metabolites can cause direct DNA toxicity by binding to and inducing DNA strand breaks, chromosomal aberrations, and micronuclei formation primarily in the epithelial cells of the mouth[13]. Micronuclei are small cytoplasmic fragments of chromosomes that form when chromosomes fail to be included in the nucleus during cell division. Due to this, they serve as a marker for genomic instability and DNA damage. The chronic exposure causes fibroblast proliferation, eventual cellular senescence or cessation of cell division,

and facilitates the accumulation of new mutations as the DNA is exposed to more of the nucleases in the cytoplasm[14]. Arecoline is additionally linked to the dysregulation of tumor protein 53 (TP53). Arecoline chronically activates TP53 which binds directly to the DNA of cells and activates pro-apoptotic genes. After an extended period of chronic activation, Arecoline has shown to cause deactivation of TP53 in causing cell death of mutated cells. As such, this creates an optimal environment for malignant cells to grow[15]. Beyond oxidative damage as described earlier, betel nut-induced hypoxia is another mechanism which induces angiogenesis and fibrosis resulting in malignant transformation. Long-term exposure of arecoline to the oral cavity results in epithelial mesenchymal transition, a process by which epithelial cells lose their characteristics and transform into more mobile and invasive cells[5]. The major biological mechanisms underlying betel nut-induced carcinogenesis are summarized in Table 1.

Epidemiological evidence

The vast incidence and prevalence of betel nut use has not waned over the decades. Even with implementation of initiatives targeting their widespread use and discussing apparent health risk, use is still persistent among a multitude of nations and demographics. A close examination of the epidemiology of oropharyngeal cancer can help to quantify the risk of betel nut use. The primary malignancy associated with betel nut use includes oral squamous cell carcinoma (OSCC)[15-17]. In Natal, South Africa, 93% of women who were diagnosed with OSCC also habitually chewed betel nuts. An odds ratio calculated from the data was 43.9, indicating a strong association between chewing and OSCC[9]. As previously explained, betel nut use can also result in the formation of precancerous lesions such as oral submucous fibrosis[11,14]. Data from multiple countries of high use displayed a submucous fibrosis prevalence of 5% among individuals who chewed betel nuts[18]. Development of oral submucosal fibrosis and OSCC displays a dose-dependent relationship with individuals who chew more betel nuts being more likely to develop these lesions. Betel quid chewing without tobacco showed a 5-fold increase in the risk of oral cancer, while adding tobacco increased the risk to 10-fold[10].

A dose-dependent relationship also exists between betel nut use and the development of other cancers. Case-control studies in Assam, India have demonstrated that betel quid chewing is additionally an independent risk factor for the development of esophageal cancer[19]. Cohort studies have also displayed a similar dose-dependent correlation in the development of liver, lung, larynx, and pancreatic cancers due to betel nut; however, causality has not yet been established[20]. A summary of key epidemiological studies examining the association between betel nut use and malignancy is provided in Table 2.

Synergistic risk factors

While betel nut use alone has been linked with increased oral malignancies, other factors such as smoking and alcohol alone are shown to have an attributable risk of oral cancer of more than 80% and have also been found to amplify the risk of developing oral cancer significantly with concurrent betel nut use[19-21]. Smoking tobacco increases the toxicity of the betel quid due to several different possible mechanisms. First, the

Table 1. Biological mechanisms of betel nut-induced carcinogenesis

Mechanism	Key compound/ factor	Pathophysiology	Cellular effect	Clinical outcome	Ref.
Epigenetic changes	Arecoline metabolites	DNA methylation and gene regulation changes	Tumor suppressor gene silencing	Cancer progression	[5]
Chronic inflammation	Cytokines (IL-6, TNF-α)	Persistent inflammatory signaling	Tissue injury, immune dysregulation	Fibrosis and tumor development	[6]
Oxidative stress	Reactive oxygen species (ROS), slaked lime	Increased free radical production	Lipid peroxidation, DNA damage	Tumor progression	[7]
Epithelial–mesenchymal transition (EMT)	Arecoline	Loss of epithelial characteristics	Increased cell migration and invasiveness	Metastasis	[7]
Synergistic carcinogenesis	Tobacco-derived nitrosamines	Combined toxic exposure	Enhanced mutagenesis	Increased cancer risk	[10]
DNA damage	Arecoline, nitrosamines	Direct DNA strand breaks and adduct formation	Chromosomal instability, micronuclei formation	Initiation of carcinogenesis	[13]
Fibrosis	TGF-β activation	Collagen deposition, fibroblast proliferation	Oral submucous fibrosis	Premalignant lesion	[14]

Table 2. Epidemiological evidence linking betel nut use to malignancy and premalignant conditions

Study Year	Location	Population	Exposure	Outcome	Key findings
Warnakulasuriya and Chen[9] 2022	South Africa (data cited)	Women with OSCC	Betel nut chewing	Oral cancer	93% of cases were habitual users
Gupta and Johnson[10] 2014	South Asia and Pacific	Multiple studies	Betel quid (± tobacco)	Oral cancer	OR~5.3 without tobacco; up to ~9–10 with tobacco
Jasim et al.[16] 2024	Southeast Asia and Pacific	Regional populations	Betel quid use	Oral malignant and premalignant disorders	Strong association with both lesion types
Hernandez et al.[17] 2017	Pacific Islands	Betel nut users	Betel chewing	Oral premalignant lesions	Increased lesion prevalence; microbiome changes
Sinha et al.[18] 2022	Multi-country	Betel nut users	Areca nut use	Oral submucous fibrosis (OSMF)	Prevalence ~5% among users
Phukan et al.[19] 2001	India	Adults	Betel + tobacco chewing	Esophageal cancer	Significantly increased risk vs non-users
Wen et al.[20] 2010	Taiwan	General population	Betel quid + smoking	Multi-site cancers	Increased risk across multiple cancer sites; interaction with smoking
Rumgay et al.[26] 2024	Global	Global populations	Areca nut + smokeless tobacco	Oral cancer burden	High population attributable fraction in Asia-Pacific
Lee et al.[27] 2012	Asia (multi-country)	Large population	Betel quid use	Oral premalignant disorders	High population burden across regions

location of the tobacco in the mouth undergoes keratinization due to friction and, with chronic use, results in the deepening of mucosal keratosis and the formation of plaques. This process may be accelerated by the mechanical action of chewing the betel quid[22]. Another possible mechanism suggests that chewing betel nuts and tobacco will increase the amount of nitrosamines and oxidative stress as well as having a synergistic effect on the betel quid cytotoxicity[23].

Alcohol use has also been shown to synergistically increase the risk of developing oral cancer in those who use betel nuts. Chronic alcohol use causes atrophy of the oral mucosa, which can be further damaged by chewing the betel quid. Alcohol can also increase the permeability of the oral mucosa and lead to increased absorption of the arecoline, leading to increased fibrotic tissue. Another possible mechanism for the synergistic effect of alcohol and betel nut use includes the alteration of the oral microbiome, which affects the body's ability to regulate its immune system[24].

Betel nut use is also linked to genetic factors that increase the user's susceptibility to oral cancer; this is suggested by the fact that only a proportion of users will develop cancer. Therefore, various genetic factors can be analyzed to find commonalities among exposed individuals who are diagnosed with cancer. Individual susceptibility is predicated on several variables such as the difference in metabolism that affects the metabolic activation of carcinogens from the betel nut, the masticator's health, and amount of nutrition, what proto-oncogenes and tumor suppressor genes are expressed, and the function of DNA repair pathways. Additionally, genetic polymorphisms can cause various phenotypic or metabolic variations that have been associated with an increased risk of developing cancer in betel nut users. Several prominent polymorphisms in a few genes have been identified such as DNA repair genes, XRCC4 in the Taiwanese population and genes encoding detoxifying enzymes GSTT1 and GSTM1 in Indian and Thai populations[25].

Another synergistic risk factor associated with betel nut use is poor oral hygiene and nutrition. A close comparison of oral hygiene was performed between those who did or did not use betel nuts and it found that despite having about the same oral hygiene methods, the individuals who used betel nuts were found to have a poorer oral health status than the non-users. This indicates the role of betel nuts in the deterioration of health gums. Additionally, other findings are more common in betel nut users such as periodontal pockets, gingival lesions, and increased calculus formation[24].

Global burden and public health

The highest rates of use of betel nuts include areas in southcentral Asia, southeast Asia, and Melanesia while the proportion of oral cancers that can be attributed to betel nut use is highest in Melanesia, Micronesia, and Polynesia and then southcentral Asia and southeastern Asia. Of these areas, countries such as Bangladesh, India, Pakistan, and Papua New Guinea were indicated to have the highest use of betel nuts as well as the highest rates of oral cancer.

When examining the prevalence of betel nut use and the risk of oral cancer, a population attributable fraction (PAF) was identified. Among males, the PAFs were highest in those found in Papua New Guinea, followed by Afghanistan, Uzbekistan, Tajikistan, and Myanmar, and in women, the highest PAFs were found in Papua New Guinea as well, followed by Bangladesh and Myanmar[26]. In general, males or those who live in lower income countries are more likely to use betel nuts and subsequently to develop oral cancer[27].

While there is a noted economic contribution of betel nut consumption, there is a more profound economic burden due to the increased health costs of cancer, loss of life, and reallocated national resources. In 2016, about 25000 cases of betel nut-related oral cancer were found in the Hunan province of China, which was estimated to cause about five billion yen (or about $34.5 million) in financial loss; in 2030, it is estimated to cause about 64 billion yen (or $442 million) in damages[28]. Additionally, healthcare costs extend beyond oral cancer alone: a meta-analysis of betel quid chewers found significantly elevated risk of obesity, metabolic syndrome, diabetes, cardiovascular disease, and all-cause mortality compared to non-chewers, adding further healthcare burden independent of cancer treatment costs[29].

Surrounding a cancer diagnosis, there is a negative stigma which could cause under-reporting of cases. The stigma stems from various explanations, such as the detriment of the diagnosis on every aspect of the patient's life or the discrimination they may face with this new label of being someone with cancer. Some people refuse to go through cancer screening because only 50% believe that cancer is curable, but others do not acknowledge the possibility of cancer as some believe that cancer is a result of karma, an aspect the individual would not want to advertise to others in their community[30].

Prevention and policy measures

Since 1985, betel nuts have been labelled as carcinogenic; however, it was not until 2004 that they were described as a Group 1 carcinogen by the World Health Organization (WHO)[9]. Since this determination, countries have been slow to regulate betel nuts or issue formal warnings of the dangers of its use. Countries like Taiwan are working on implementing regulations towards the use and sale of betel nuts, but they face challenges such as the cultural significance of the betel nut. Historically, the betel nut was perceived as a high-end commodity that only individuals of certain wealth could obtain. Now, many fear social isolation if they attempt cessation of betel nut use. Other reasons that contribute to the resistance of implementing regulations towards a highly regarded habit include lack of awareness towards the risk of using betel nut even without tobacco or lime, dependence to get through the long work day, and barriers towards attending cessation programs (i.e. difficulty getting time off of work, language barrier)[31].

In the United States, betel nuts are not banned federally and are often sold in ethnic markets. The USDA and FDA have no specific regulations for the importation of betel nut and shipments only tend to be flagged if they are an undeclared color, combined with artificial sweeteners, or combined with tobacco. If combined with tobacco, then the betel nut product is inspected with the same regulations in place for smokeless tobacco such as an age minimum and sampling/testing if deemed necessary[3].

The lack of stricter oversight by the FDA creates a lack of awareness about the health consequences of chewing betel nuts in addition to difficulty regulating consumption. Areas of the greatest betel nut consumption in the United States are high-risk immigrant populations, including individuals who identify as South Asian or Pacific Islander, who are greatly under-recognized[32]. As these populations increase in size in the United States, it will become even more important to educate these communities about the many risks of betel nuts and to implement resources to support those who consume them. One consequence of the lack of oversight is how betel nut products can be marketed online to those of all ages and dispersed without regular sampling and testing[4]. On top of FDA regulations, some states have developed additional restrictions on the sale and use of betel nut products due to the lack of federal regulation. For example, in New York, betel nut products with any tobacco can only be sold in tobacco shops, and in Ohio, law specifically states that betel nut use with or without tobacco is not permitted. Additionally, some states such as Oregon have passed bills to implement community-based campaigns and healthcare worker training in order to increase awareness of the negative effects of betel nuts[3]. The bill in Oregon, house bill 3511, passed in February 2025, so the impact is not widely documented or confirmed. However, it is recommended that additional oversight such as minimum legal age and price sales and banning self-service displays across all states be implemented to prevent the short- and long-term effects of betel nut use.

Gaps in current research

There are several gaps in the current research of betel nut use in South Asian and Pacific Islander populations. This can largely be attributed to limited data from areas with a high prevalence of betel nut users; furthermore, very few cohort studies have been performed long-term, making it difficult to understand the full extent of the health dangers of betel nuts. Studies may also have reduced generalizability due to

the cultural and genetic differences of the many groups who use betel nuts. Populations found in more Western countries who have immigrated from areas that have more frequent betel nut use go understudied and under-recognized due to an even greater lack of awareness of the negative effects of betel nut use. Another gap includes the need for more specific, identifiable biomarkers as well as an improved molecular understanding of the damage caused by betel nuts.

CONCLUSION

Betel nuts are commonly used in cultural and social practices in South Asia and the Pacific Islands. These products have been associated with an increased risk of oral cancer as well as hepatic and pancreatic cancer due to oxidative stress, DNA damage, and chronic inflammation. Despite the FDA's designation of betel nuts as a Group 1 carcinogen, there are few federal regulations, leaving the sale and use of betel nut products largely up to the states. While some states have implemented limitations and community campaigns to reduce the use of betel nuts, these strategies are few and far between. Due to the limited research on these populations in the United States, it is difficult to discern the exact impact of these new state policies on those who use betel nuts. Limited long-term cohort studies have been performed but have reduced generalizability due to the variety of risk factors and genetic factors as well as the cultural impact of betel nuts within a community. Therefore, it is necessary to implement more public health programs to increase the awareness of the dangers of betel nut use in addition to oral cancer screening and more robust research on the health consequences of betel nut use.

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CONFLICTS OF INTEREST
The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

FUNDING
There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT
Ethical approval and informed consent were not required for this study.

AUTHORS' CONTRIBUTIONS
AE, NS and BM: conceptualization, data curation, project administration, writing of original draft. TP and AA: formal analysis, visualization, writing, reviewing and editing of the manuscript. DD: supervision, validation, writing, reviewing and editing of the manuscript. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY
Data sharing is not applicable to this article as no new data was created.

PROVENANCE AND PEER REVIEW
Not commissioned; externally peer-reviewed.