CENTER FOR GLOBAL HEALTH

Areca Nut and Betel Quid: Biological Mechanisms of Disease

Betel Quid Constituents and Carcinogens

The ingredients and combinations of betel quid differ across the world. The major constituents of a betel quid may include areca nut, *Piper betle* L. (betel leaf, inflorescence, and/or stem), slaked lime, tobacco, catechu, spices (e.g., cloves, cardamom, aniseed), sweeteners (e.g., coconut, dried dates), and essences (e.g., menthol, mint, rose essence) (IARC, 2004).

Areca nut, the main component of betel quid, is classified as carcinogenic to humans, as are betel quid with and without tobacco (IARC, 2004). The chemical composition of areca nut includes polyphenols (flavonols, tannins), alkaloids (e.g., arecoline, arecaidine, guvacine, guvacoline), and other elements (e.g., sodium, magnesium, chlorine, calcium, copper, bromine) (IARC, 2004).

The systemic effects of areca nut are mainly due to the principal alkaloid arecoline (Garg et al., 2014).

Biological Mechanisms of Disease and Disease Outcomes

Betel quid and areca nut have been associated with disease outcomes that affect nearly all human organs and systems, including:

- Brain
- Heart
- Lungs
- Endocrine system
- Immune system
- Gastrointestinal tract
- Reproductive organs

Areca nut has been shown to cause or worsen conditions such as myocardial infarction, cardiac arrhythmias, asthma, central obesity, type II diabetes, metabolic syndrome, hypothyroidism, and infertility (Garg et al., 2014).

Oral and Other Cancers. Risk for cancer, especially oral cancer, is associated with betel quid use in some Asian and Pacific regions (Gupta & Johnson, 2014). Betel quid chewing, with added tobacco, increases the relative risk of oral/oropharyngeal cancer, a risk that is much higher in women than in men (Guha et al., 2014). Adding tobacco also increases the risk of cancer of the pharynx and upper gastrointestinal tract (Molin & Plewig, 2007). Compounds in the areca nut can alkylate the genetic material (DNA), triggering changes that can increase the risk of cancer (Hu & Chao, 2012). Constituents such as tobacco, areca nut, and lime remain in contact with the gums, inner lining of the mouth, and tongue for many hours, increasing the risk for cancer.

Periodontal Disease. Chewing betel quid and areca nut have been shown to lead to discoloration of teeth; development of chronic debilitating diseases involving the gingival and oral mucosa, such as oral submucous fibrosis (OSF) and leukoplakia; and higher mortality (Shiu & Chen, 2004; Ariyawardana et al., 2006; Mazahir et al., 2006). Betel chewing has been shown to predispose users to periodontal disease, and people with periodontal disease are more likely to test positive for Helicobacter pylori (H. pylori) bacteria (Fernando et al., 2009). Arecoline is cytotoxic to human gingival fibroblasts; repeated and long-term exposure to arecoline could impair the gingival fibroblast functions (Y. C. Chang et al., 2001). During betel quid chewing, areca nut components can induce endothelial damage which is associates with the pathogenesis of OSF and periodontitis (Tseng et al., 2012).

Reproductive health and birth outcomes. Areca nut chewing alone, or with tobacco or other ingredients, can be toxic to reproductive health. Use of these products during pregnancy can have adverse effects on pregnancy and its outcome (Kumar, 2013). In India, for example, pregnant women who used areca nut products were found to have a threefold increased risk of stillbirth as well as an increased risk of having low birth weight infants (Gupta & Ray, 2003). These fetal effects are likely due to the direct stimulation of the central nervous system by arecoline, resulting in reduced maternal–fetal blood flow (S. K. Lin et al., 2002).

Obesity and cardiovascular disease. Areca nut chewing is closely associated with obesity, possibly because of the increased appetite of areca nut chewers (W. C. Chang et al., 2006). Areca chewing with or without tobacco has also been associated with increased risk of cardiovascular disease and may impose a greater risk for cardiovascular disease than smoking (Zhang et al., 2010). Greater appetite and glucose intolerance resulting from areca nut chewing may play a key role in the development of related diabetes and enhance oxidative stress, increasing the risk of cardiovascular disease (W. Y. Lin et al., 2008).

Epidemiology of Areca Nut and Betel Quid

Global Epidemiology of Use

Areca nut is used by approximately 600 million people worldwide (10–20% of the world's population), most often as a component of betel quid (Gupta & Warnakulasuriya, 2002). India is home to the largest areca-consuming population in the world. Patterns of use change over time, and variations in products and patterns of use differ across countries. Although areca nut use is declining in some countries, such as Thailand, evidence suggests that its use is increasing in other countries, such as in India and Taiwan (Gupta & Warnakulasuriya, 2002).

Table 1 demonstrates the percentage of adults in select South-East Asian countries who currently used smokeless tobacco between 2006 and 2010. In some countries, including Bangladesh and Thailand, women use these products more than men.

Table 1. Percentage of Adults (≥15 years) Who Currently Used Smokeless Tobacco in the South-East Asia Region, 2006–2010

Country	Year	Age group (years)	Total (%)	Men (%)	Women (%)
Bangladesh*	2009	15+	27.2	26.4	27.9
Bhutan† (subnational)	2007	25–74	19.4	21.1	17.3
India*	2009	15+	25.9	32.9	18.4
Maldives‡	2009	Men, 15–64; Women, 15–49	—	6.0	4.2
Myanmar†	2009	15–64	29.6	51.4	16.1
Nepal§	2008	15–64	18.6	31.2	4.6
Sri Lanka†	2006	15–64	15.8	24.9	6.9
Thailand*	2009	15+	3.9	1.3	6.3
Timor-Leste‡	2009–2010	15–49	—	2.5	1.9

Source: NCI and CDC, 2014. *Global Adult Tobacco Survey, 2009, from Centers for Disease Control and Prevention, cited 2012. †WHO STEPS, 2006–2009, from: World Health Organization, 2011. ‡Demographic and Health Surveys, 2009–2010, from Kishor et al., 2014. §Individual country surveys, from World Health Organization, 2011.

Changing Epidemiology of Related Neoplasia

The prevalence of oral cancers and related neoplasia is high in Asian countries, especially in South and South East Asia (Rao et al., 2013). Comprehensive reviews have found that the tongue is the leading site of oral cancers in India, with the next most common sites in Asian countries including the buccal mucosa and gingiva. Betel quid chewing, tobacco smoking, and alcohol have been cited as the main reasons for the increasing incidence rates (Rao et al., 2013). Research also indicates that there is extensive misinformation and a general lack of awareness about the risk factors and signs of oral cancer among South Asian migrant communities (Shetty et al., 1999).

Use Among Migrant Populations

Studies of migrant populations are of considerable interest to epidemiologists in determining the impact of such environmental exposures. Studies on Asian migrants residing in the United Kingdom have shown that consumption of areca nut and betel quid is highly prevalent in these new communities. Evidence indicates that as areca nut users migrate to other countries and communities, their patterns of use are closely similar to the local chewing customs prevalent in their countries of origin, as are the related disease outcomes. For example, there is a high incidence of cardiovascular disease, oral cancer, hypertension, and late onset diabetes among Indians living in the United Kingdom (Warnakulasuriya, 2002).

Surveillance Systems

As a part of strategy to implement the provisions of the WHO Framework Convention on Tobacco Control (WHO FCTC), tobacco surveillance was established to support tracking and monitoring of tobacco use and its related indicators. Currently, several surveillance systems on betel quid and general smokeless tobacco use exist, including the Global Adult Tobacco Surveys (GATS), the Global Youth Tobacco Surveys (GYTS), the WHO STEPwise Approach to Surveillance surveys (WHO STEPS), and the Demographic and Health Surveys (DHS) (NCI & CDC, 2014).

Systematic global tobacco surveys are important tools for measuring the prevalence of betel quid use and key policy indicators. While the existing surveys and systems provide helpful information on betel quid use, further refinement is warranted. Potential enhancements to the surveillance systems include standardization of implementation across countries, increased precision, longitudinal studies, and larger sample sizes.