Betel nut chewing in high-income countries—lack of awareness and regulation

Geoff Kidd/Science Photo Library

The areca nut is the seed of the areca palm (*Areca catechu*), which grows in Asia, the tropical Pacific, and parts of east Africa. It is commonly referred to as betel nut, because it is often chewed while wrapped in betel leaves. It is the fourth most widely used addictive substance worldwide and is chewed regularly by at least 10% of the world population.[1,2] In 2004, the International Agency for Research on Cancer stated that chewing betel nut is carcinogenic to humans (it is a group 1 carcinogen) and is an independent major risk factor of oral cancer.[3] Areca nut and betel quid are also commonly mixed with tobacco.[4]

Betel nut is mainly chewed in Asian countries, but it is also chewed in New Zealand, Australia, the USA, and the UK by immigrants from India and other parts of Asia. Hence, although betel nut consumption is highly prevalent in Asia, this substance poses a global health challenge.[5] Betel nut is often served as industrially prepared cheap ready-to-chew mixtures in small, colourful sachets. In the UK it can be purchased as a single product from local vendors (so-called paan shops) in areas with a high proportion of Asian communities (eg, Wembley, Harrow, Ilford, and Southall in London, and similar regions in Leicester, Birmingham, Manchester, and Leeds), or simply purchased online on popular trading platforms. Notably, none of the information on these websites nor the packaging contain any information about the carcinogenic effects and the risk of oral cancer, by contrast with warning labels on tobacco products in line with the Tobacco Products Directive (from the WHO Framework Convention on Tobacco Control).[6] These products are also not subject to any other form of regulation in the UK.

Prevalence data about betel nut chewing among Asian communities in the UK are limited. To get an idea about the prevalence of betel nut chewing and the community's awareness of its carcinogenic risks, we did a short survey in a sample of the Indian community in the UK (n=125; table). Data collection was anonymised and no vulnerable participants were involved. Upon advice from University College London Research Ethics Committee and Harrow National Health Service (NHS) Research Ethics Committee, the survey was exempt from requiring a research ethics committee. A cross-sectional survey with secure data storage to gather anonymous data was done online after members of the Indian community were approached via a newsletter. After a recorded consent process, the questionnaire asked 23 close-ended questions covering demographics, knowledge of the carcinogenicity of areca nut, and areca nut and tobacco usage.

The survey showed that 79 (74%) of 107 participants consumed betel nut once or more times in their lifetime, more than half (60 [56%]) consume betel nut once or more times a year, and around a quarter (28 [26%]) consume betel nut once or more times a month. Crucially, consumers are significantly less aware that chewing betel nut can cause cancer ($p=0{\cdot}00626$, Pearson's χ^2 test). There were no significant associations between betel nut consumption and age, sex, salary, education, or marital status (data not shown). Moreover, in a recent survey[7] of primary care physicians in the UK, more than a quarter of general practitioners (GPs) were unaware of betel nut being a risk factor for throat cancer.

Taking all this into consideration, current data suggest that a substantial proportion of members of Asian communities in the UK chew betel nut. Many of the consumers are unaware of its carcinogenic potential. Moreover, GPs, as their first point of call, might also be unaware of the cancer risks and might only ask about smoking and alcohol intake when risk-stratifying patients, meaning that the threshold for an urgent referral to a specialist centre could be higher.

Oral cancer is one of the most preventable cancers, and awareness and screening campaigns have shown a decrease in its incidence.[8] Given that betel nut is not typically discussed within the setting of migrant populations, we strongly recommend the introduction of awareness campaigns among members of Asian communities across the UK and among GPs. To address the lack of regulation, ease of access and low price point, MPOWER tobacco control guidelines (including economic guidelines)[9] should be extended and followed. Indeed, given the similar risks and the urgent need for a

	Study population with complete data (n=107)
Age, years	
30–39	3 (3%)
40–49	12 (11%)
50–59	29 (27%)
60–69	42 (39%)
≥70	21 (20%)
Sex	
Male	79 (74%)
Female	28 (26%)
Marital status	
Married	93 (87%)
Not married	12 (11%)
NA	2 (2%)
Area of residence	
Buckinghamshire	1 (1%)
Cambridgeshire	1 (1%)
Essex	11 (10%)
Fermanagh	1 (1%)
Herefordshire	3 (3%)
Hertfordshire	13 (12%)
Kent	2 (2%)
Lancashire	1 (1%)
Leicestershire	3 (3%)
London or greater London	25 (23%)
Middlesex	28 (26%)
Norfolk	1 (1%)
Northamptonshire	2 (2%)
Oxfordshire	1 (1%)
Surrey	5 (5%)
Warwickshire	3 (3%)
NA	6 (6%)
Level of education	
A level, International Baccalaureate, or equivalent	24 (22%)
Attended school but not completed GCSE, or equivalent	8 (7%)
Bachelors degree and above	54 (50%)
GCSE or equivalent	17 (16%)
Never attended school	1 (1%)
NA	3 (3%)
Race	
Asian and Asian British	106 (99%)
Prefer not to answer	1 (1%)
Income (GBP)	
10001–20000	15 (14%)
20001–30000	21 (20%)
30001–50000	15 (14%)
50001–70000	14 (13%)
70001–100000	9 (9%)
<10000	8 (7%)
>100000	17 (16%)
NA	8 (7%)
Chewing tobacco	
Yes	6 (6%)
No	100 (93%)
NA	1 (1%)
Smoking tobacco	
Yes	11 (10%)
No	96 (89%)

NA=not applicable. GCSE=General Certificate of Secondary Education.

Table: **Demographics of the study population**

regulatory context, we call on WHO to consider including other cancer-related addictive substances commonly mixed with tobacco, such as betel nut, under a broader Framework Convention on Tobacco Control, as previously highlighted by *The Lancet Oncology*.[10] Similar to tobacco, a focus on regulation and awareness initiatives for betel nut (eg, package labelling), will be key in helping to address this urgent public health challenge. Furthermore, we urge the consideration of evidence-based risk-stratified screening approaches for oral cancer, ideally led by dentists or primary care physicians with information provided in multiple languages, such as an online tool or app that can be used by members of the public, GPs, and dentists to prevent both pre-cancerous lesions, such as oral submucous fibrosis, erythroplakia, and leukoplakia, and to decrease the incidence of oral cancer among Asian communities in the UK. In conclusion, we call for the implementation of all these measures as part of tobacco control policy as policymakers, researchers, and clinicians will gain from working together in a pre-implemented framework to reduce the morbidity and mortality associated with betel nut consumption.

*Matt Lechner, Charles E Breeze, Francis Vaz, Valerie J Lund, *Bhik Kotecha
UCL Cancer Institute, University College London, London, WC1E 6DD, UK (ML, CEB); Royal National Throat, Nose and Ear

Hospital (ML, VJL, BK) and Head and Neck Centre (ML, FV), University College London Hospitals NHS Trust, London, UK; and Royal London Hospital, Barts Health NHS Trust, London, UK (ML)
m.lechner@ucl.ac.uk; bhik.kotecha@nhs.net

ML and CEB contributed equally. We declare no competing interests. We acknowledge invaluable support from the Association for the Global Advancement of Ear, Nose, and Throat Surgery, and Head and Neck Cancer Research (AGA-ENT; charity number 1165453) and the American Head and Neck Society (AHNS International Outreach Cancer Prevention Grant).

1 Secretan B, Straif K, Baan R, et al. A review of human carcinogens—part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009; **10:** 1033–34.
2 Gupta PC, Warnakulasuriya S. Global epidemiology of areca nut usage. *Addict Biol* 2002; **7:** 77–83.
3 IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 85: betel quid and areca-nut chewing and some areca-nut-derived nitrosamines. Lyon: International Agency for Research on Cancer, 2004.
4 Warnakulasuriya S, Trivedy C, Peters TJ. Areca nut use: an independent risk factor for oral cancer. *BMJ* 2002; **324:** 799–800.
5 Mehrtash H, Duncan K, Parascandola M, et al. Defining a global research and policy agenda for betel quid and areca nut. *Lancet Oncol* 2017; **18:** e767–75.
6 WHO. WHO Framework Convention on Tobacco Control . Geneva: World Health Organization, 2003.
7 Lechner M, Vassie C, Kavasogullari C, et al. A cross-sectional survey of awareness of human papillomavirus-associated oropharyngeal cancers among general practitioners in the UK. *BMJ Open* 2018; **8:** e023339.
8 Petersen PE. Oral cancer prevention and control—the approach of the World Health Organization. *Oral Oncol* 2009; **45:** 454–60.
9 WHO. MPOWER: a policy package to reverse the tobacco epidemic. Geneva: World Health Organization, 2008.
10 The Lancet Oncology. E-cigarettes–new product, old tricks. *Lancet Oncol* 2018; **19**: 1543.

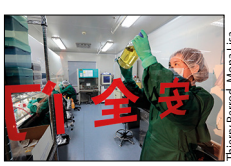
Challenges in anticancer drug R&D in China

The availability of innovative drugs in China has long been compromised by the so-called drug lag, in which a lengthy drug review processes, scarcity of domestically developed innovative drugs, overly strict policies in clinical trial application, and import drug registration has impeded drug innovation.[1,2] To tackle this dilemma, the Chinese Government has issued a series of regulatory reforms on drug administration since 2017.[3-7] The changing landscape of drug research and development (R&D) in China is captured by an annual report of China's phase 1 oncology studies (appendix).

The report shows that there were 180 phase 1 oncology trials done in mainland China in 2017, making it the second highest region for phase 1 oncology trials second to Europe (n=241). However, despite the boom in phase 1 studies, there has been a paucity of experienced and fully equipped study sites and a severe inequality in the geographical distribution of studies done across China. 180 phase 1 trials were done in only 18 facilities (figure), 107 (59%) of which were finished by five study sites only. 132 (73%) of these studies were done in either Beijing, Shanghai, or Guangzhou, the three biggest cities in China. The rest of the studies were also done in major cities in China. This imbalanced distribution of phase 1 study sites partly reflects the disparities in medical resources between regions in China.

Collaboration and communication between different study sites, sponsors, and contract research organisations is difficult and rare to come by. For multicentre phase 2–3 studies, the strategy of building a collaborative group has shown to work. For example, the China Thoracic Oncology Group, which was founded in 2007, is a network dedicated to the development of phase 2–3 studies in lung cancer and contributed to the OPTMAL[8] and INFORM[9] trials, two multicentre, randomised, phase 3 studies that respectively established the standard first-line and maintenance therapy for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer. However, more than 10 years later, no such organisation exists for phase 1 studies in China.

Repetitive study designs in phase 1 trials is another problem that could compromise China's agenda to become the global engine of drug innovation. Of the 180 phase 1 studies that were done in 2017, 21 (12%) were bioequivalence or bioavailability studies of generic drugs, 67 (37%) were pharmacokinetic or pharmacodynamic studies, 76 (43%) investigated drug tolerability, and only 16 (9%) were first-in-human studies of innovative treatments. Trials sponsored by multinational biopharmaceutical companies are all pharmacokinetic or pharmacodynamic studies that aim to characterise the pharmacokinetic and pharmacodynamic profile of the drug for the Chinese population. Nine of the 19 trials sponsored by multinational pharmaceutical companies were pharmacokinetic or pharmacodynamic bridge studies that merely serve to accelerate regulatory approvals in China. Bridge studies are relatively small-scale studies that investigate the differences in pharmacokinetic, pharmacodynamic, and clinical properties of a drug. With these studies, foreign clinical data can be used to


Thierry Berrod, Mona Lisa Production/SPL

See Online for appendix