Research Article

Association Between Betel Nut Chewing And Oral Squamous Cell Carcinoma: A Hospital-Based Retrospective Study

Saiful Azam[1], Fatema Tuz Juhura[2,] S M Yunus Ali[3], Azmira Khatun[4], Immam Hossin[5], Rasel Ahmad[6]

1. Associate Professor, Department of Oral and Maxillofacial Surgery, Bangladesh Medical University, Dhaka, Bangladesh. Email Id: saifulbds75@gmail.com, Orcid Id: 0009-0003-7469-6346.
2. Dental Surgeon, FCPS, Trainee, Bangladesh Medical University, Dhaka, Bangladesh. Email Id: dr.tonmoy@gmail.com .Orcid Id:
3. Associate Professor, Department of Urology, Bangladesh Medical University, Dhaka, Bangladesh. Email Id:dryunusuro@gmail.com.Orcid Id: 0009-0007-9348-3417
4. Medical Officer, Department of Surgical Oncology, Bangladesh Medical University (BMU), Dhaka,Bangladesh. Email Id: dr.azmira@bmu.ac.bd .Orcid Id:
5. PhD Fellow, Bangladesh Medical University, (OSD), DGHS, Mohakhali, Dhaka, Bangladesh. Email Id: bulbulbds42@gmail.com, Orcid Id: 0009-0002-8712-178X.
6. Assistant Professor, Medical Education, Department of Public Health and Informatics, Bangladesh Medical University, Dhaka, Bangladesh. Email Id: raselbds42@bsmmu.edu.bd. Orcid Id:0009-0009-2936-0169

Corresponding Author: Dr. Md. Rasel Ahmad, Assistant Professor, Medical Education, Department of Public Health and Informatics, Bangladesh Medical University, Dhaka, Bangladesh.

ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is a major health problem in South and Southeast Asia linked to betel nut chewing, but detailed evidence on exposure patterns and independent risk is limited. This study assessed the association between betel nut chewing habits and OSCC, focusing on exposure and risk factors. **Methods:** A retrospective case–control study at Bangladesh Medical University in Dhaka (January 2024–January 2025) included 180 participants: 90 OSCC cases confirmed histopathologically and 90 controls. Data via questionnaire covered sociodemographics, betel nut chewing, betel quid use, smokeless tobacco, smoking, alcohol, and exposure duration and frequency. Chi-square tested associations, and multivariable logistic regression identified independent OSCC predictors. **Results:** Betel nut chewing was significantly higher in OSCC cases (80.0%) compared to controls (51.1%). Betel quid use (areca nut with tobacco) showed an even stronger association (66.7% vs 40.0%). Long-term chewing (>10 years) was more common among OSCC cases (64.4%). Multivariable analysis revealed that betel quid use (AOR = 4.15, $p < 0.001$), betel nut chewing (AOR = 3.42, $p < 0.001$), and duration >10 years (AOR = 2.96, $p = 0.001$) were significant independent predictors of OSCC. Smoking was also associated with increased risk (AOR = 1.88, $p = 0.046$), while alcohol consumption was not statistically significant. Increasing age and male gender were additionally identified as risk factors. **Conclusion:** Betel nut chewing, especially with tobacco, is a significant risk factor for OSCC. Urgent public health measures are needed to reduce areca nut use and lower oral cancer in high-risk groups.

Keywords: Betel nut chewing, OSCC, betel quid, smokeless tobacco, risk factors,retrospective case–control study.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) continues to pose a significant global public health issue, notably in regions where betel quid chewing, classified as a Group 1 carcinogenic exposure, is prevalent [1]. In the year 2020, over 377,000 new cases were documented worldwide, with projections suggesting a 40% increase by the year 2040 [2]. While tobacco and alcohol are well-recognized etiological factors, products containing areca nut remain a predominant risk factor for oral malignancies particularly in South and Southeast Asia [3,4]. Despite the established association, there are ongoing inconsistencies in the reporting of specific exposure patterns and anatomical subsites within the existing literature [5], further complicated by underreporting within regional cancer registries [6].

Betel quid contains biologically active alkaloids such as arecoline, which induce fibrotic and carcinogenic changes within the oral mucosa, particularly in the gingivo-buccal region [7]. The synergistic interaction of areca nut with tobacco and alcohol further amplifies mutagenic potential, contributing to more aggressive disease phenotypes and poorer clinical outcomes [8]. However, despite increasing recognition of these mechanisms, limited clinical evidence exists linking specific chewing behaviors including duration, frequency, and product type to tumor differentiation patterns and anatomical distribution.

Furthermore, oral submucous fibrosis (OSMF), a well-established premalignant condition strongly associated with areca nut exposure, plays a critical role in malignant transformation [9]. Yet the progression dynamics from OSMF to invasive OSCC, particularly in relation to quantified exposure levels, remain insufficiently characterised in clinical cohorts [10]. Existing studies largely emphasise mortality and incidence trends, while neglecting detailed histopathological variation and site-specific tumour behaviour associated with chronic exposure [11,12].

Emerging evidence suggests that cumulative exposure metrics, such as the “betel-year” assessment, may provide a more precise understanding of carcinogenic risk and disease progression [13]. However, standardised clinical validation of these models remains limited. Additionally, variations in tumour differentiation, nodal metastasis, and recurrence patterns between OSMF-associated and non-OSMF OSCC cases are not adequately explored in many retrospective datasets [14].

Therefore, this hospital-based retrospective study aims to evaluate the association between betel nut chewing habits and OSCC, with a specific focus on exposure patterns, duration, and clinical presentation. By integrating detailed habit history with histopathological outcomes, this study seeks to provide refined evidence on how areca nut exposure influences tumour behaviour and site-specific vulnerability.

METHODOLOGY

Study Design and Setting

This study was designed as a hospital-based retrospective analytical observational study using a case–control design to evaluate the association between betel nut–related chewing habits and oral squamous cell carcinoma (OSCC). The study was conducted at Bangladesh Medical University (BMU), Dhaka, Bangladesh, a tertiary referral center for oral and maxillofacial pathology and oncology services. The hospital maintains comprehensive clinical and histopathological records, allowing accurate identification of OSCC cases and selection of appropriate non-OSCC controls for comparative analysis of exposure patterns.

Study Period

The study was conducted over a one-year retrospective review period from January 2024 to January 2025. All eligible cases diagnosed within this timeframe were included based on medical record review and histopathological confirmation.

Study Population and Sample Size

A total of 180 participants were included in this retrospective study, consisting of 90 histopathologically confirmed OSCC cases and 90 non-OSCC controls. Controls were selected from patients treated at the same institution for non-malignant oral conditions during the same study period and were confirmed to have no clinical or histopathological evidence of malignancy. A 1:1 case–control ratio was applied to ensure comparability between groups.

Eligibility Criteria

Inclusion criteria comprised patients aged 18 years and above with complete medical records. Cases included patients with histopathologically confirmed primary OSCC. Controls included individuals without any history or evidence of oral malignancy, verified through clinical examination and hospital records. Patients with recurrent or metastatic oral cancers, incomplete exposure documentation, or missing key clinical data were excluded from the study.

Data Collection and Study Variables

Data were extracted retrospectively using a structured and pre-tested data collection form from medical records and supplemented by patient interviews when required. Information collected included sociodemographic characteristics (age, gender, and socioeconomic status) and exposure history, including betel nut chewing, betel quid use (areca nut with tobacco), smokeless tobacco consumption (pan masala/gutkha), mixed chewing habits, smoking, and alcohol intake. Duration and frequency of chewing habits were recorded to assess dose–response relationships.

Outcome Definition

The primary outcome of the study was the presence of oral squamous cell carcinoma (OSCC), confirmed histopathologically according to standard diagnostic criteria. Individuals classified as cases had confirmed OSCC, while controls were verified as free from OSCC based on clinical examination and hospital record review.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics version 27.0. Descriptive statistics were used to summarize participant characteristics and exposure variables in terms of frequencies, percentages, and where appropriate, mean ± standard deviation. Associations between categorical variables and OSCC status were assessed using the Chi-square test. To identify independent predictors of OSCC, binary logistic regression analysis was performed, and results were reported as adjusted odds ratios (AOR) with corresponding 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

Ethical approval was obtained from the Institutional Ethics Committee of Bangladesh Medical University prior to data collection. All data were handled with strict confidentiality and anonymity in accordance with institutional ethical guidelines and principles of human research.

RESULTS

Table 1 shows the sociodemographic distribution of participants in the OSCC and non-OSCC groups. Most participants were in the older age categories, especially 51–60 years (33.3% in OSCC vs 22.2% in non-OSCC),

followed by 41–50 years (27.8% vs 22.2%) and >60 years (22.2% vs 18.9%). Younger groups (≤30 and 31–40 years) were less represented, especially in OSCC. Males made up a higher proportion in both groups, with a greater male presence in OSCC (72.2%) versus non-OSCC (61.1%). More OSCC participants belonged to low SES (61.1%) compared to non-OSCC (44.4%), while non-OSCC had higher middle and high SES representation.

Table 1: Sociodemographic characteristics of study participants

Variable	Category	OSCC group n (%)	Non-OSCC group n (%)
Age (years)	≤30	5 (5.6)	13 (14.4)
	31–40	10 (11.1)	20 (22.2)
	41–50	25 (27.8)	20 (22.2)
	51–60	30 (33.3)	20 (22.2)
	>60	20 (22.2)	17 (18.9)
Gender	Male	65 (72.2)	55 (61.1)
	Female	25 (27.8)	35 (38.9)
Socioeconomic Status (SES)	Low	55 (61.1)	40 (44.4)
	Middle	25 (27.8)	35 (38.9)
	High	10 (11.1)	15 (16.7)

Table 2 shows exposure variables among OSCC and non-OSCC participants. Betel nut chewing was more common in OSCC (80.0%) than non-OSCC (51.1%). Betel quid use was reported by 66.7% of OSCC versus 40.0% of non-OSCC. Smokeless tobacco was higher in OSCC (50.0%) compared to controls (32.2%). Mixed chewing habits were in 44.4% of OSCC, and 20.0% of non-OSCC. Smoking was more prevalent in OSCC (55.6%) than non-OSCC (33.3%). Alcohol consumption was reported by 38.9% of OSCC and 27.8% of non-OSCC.

Table 2: Distribution of Exposure Variables among Study Participants

Variable	Category	OSCC group n (%)	Non-OSCC group n (%)
Betel nut chewing	Yes	72 (80.0)	46 (51.1)
	No	18 (20.0)	44 (48.9)
Betel quid use (areca nut + tobacco)	Yes	60 (66.7)	36 (40.0)
	No	30 (33.3)	54 (60.0)
Smokeless tobacco use (pan masala/gutkha)	Yes	45 (50.0)	29 (32.2)
	No	45 (50.0)	61 (67.8)
Mixed chewing habits	Yes	40 (44.4)	18 (20.0)
	No	50 (55.6)	72 (80.0)
Smoking	Yes	50 (55.6)	30 (33.3)
	No	40 (44.4)	60 (66.7)
Alcohol consumption	Yes	35 (38.9)	25 (27.8)
	No	55 (61.1)	65 (72.2)

Table 3 shows the distribution of chewing duration and frequency among study participants in the OSCC and non-OSCC groups. Most OSCC participants chewed for over 10 years (64.4%), while only 11.1% in the non-OSCC group did so. Shorter durations were more common in the non-OSCC group, with 51.1% reporting 6–10 years and 37.8% ≤5 years, versus 24.4% and 11.1% in OSCC. Daily chewing was more common in both groups but higher in OSCC (77.8%) than non-OSCC (64.4%), whereas occasional chewing was more frequent in non-OSCC (35.6%) than OSCC (22.2%).

Table 3: Distribution of Chewing Duration and Frequency among Study Participants

Variable	Category	OSCC group n (%)	Non-OSCC group n (%)
Duration of chewing (years)	≤5 years	10 (11.1)	34 (37.8)
	6–10 years	22 (24.4)	46 (51.1)

	>10 years	58 (64.4)	10 (11.1)
Frequency of chewing	Occasional	20 (22.2)	32 (35.6)
	Daily	70 (77.8)	58 (64.4)

Table 4 presents the link between betel nut–chewing and oral squamous cell carcinoma (OSCC). Betel nut was chewed by 80.0% of OSCC cases and 48.9% of controls, with a significant difference (χ^2=18.42, p < 0.001). Betel quid use (areca nut with tobacco) was seen in 66.7% of OSCC cases versus 40.0% of controls, also significantly different (χ^2=22.15, p < 0.001).

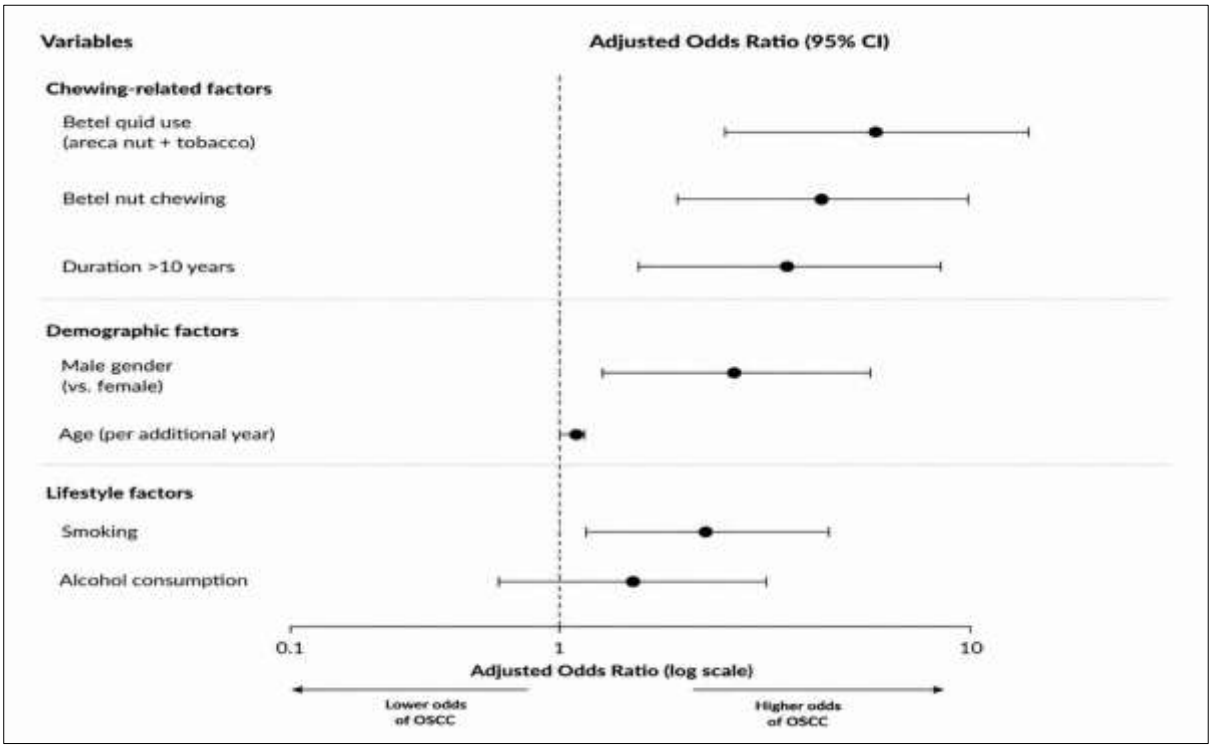
Table 4: Association between Betel Nut–Related Chewing Habits and Oral Squamous Cell Carcinoma (OSCC)

Exposure	Category	OSCC group n (%)	Non-OSCC group n (%)	χ^2	p-value
Betel nut chewing	Yes	72 (80.0)	46 (51.1)	18.42	<0.001
	No	18 (20.0)	44 (48.9)		
Betel quid use (areca nut + tobacco)	Yes	60 (66.7)	36 (40.0)	22.15	<0.001
	No	30 (33.3)	54 (60.0)		

Table 5 shows multivariable logistic regression analysis identifying independent predictors. Betel nut chewing increased OSCC odds (AOR=3.42, p<0.001). Betel quid (areca nut with tobacco) had an even stronger link (AOR=4.15, p<0.001). Chewing over 10 years raised odds (AOR=2.96, p=0.001). Smoking was significantly associated (AOR=1.88, p=0.046), but alcohol was not (AOR=1.56, p=0.172). Age increased odds slightly (AOR=1.04, p=0.012), and males had higher odds than females (AOR=2.21, p=0.017).

Table 5: Multivariable Logistic Regression Analysis Identifying Independent Predictors of Oral Squamous Cell Carcinoma (OSCC)

Variable	Adjusted OR (AOR)	95% CI	p-value
Betel nut chewing	3.42	1.78–6.58	<0.001
Betel quid use (areca nut + tobacco)	4.15	2.11–8.18	<0.001
Duration >10 years	2.96	1.52–5.75	0.001
Smoking	1.88	1.01–3.49	0.046
Alcohol consumption	1.56	0.82–2.98	0.172
Age (continuous)	1.04	1.01–1.07	0.012



Male gender	2.21	1.15–4.24	0.017

Figure I: Forest plot of independent predictors of oral squamous cell carcinoma (OSCC) identified through multivariable logistic regression analysis

Figure I shows adjusted odds ratios with corresponding 95% confidence intervals for chewing-related, demographic, and lifestyle factors. The vertical reference line at OR = 1 indicates no association. Points to the right of the reference line indicate increased odds of OSCC, while horizontal lines denote the precision of the estimates.

DISCUSSION

This hospital-based case–control study demonstrated a strong and statistically significant association between betel nut–related chewing habits and oral squamous cell carcinoma (OSCC). The findings showed that betel nut chewing, betel quid use (areca nut with tobacco), and long-term exposure were independently associated with increased odds of OSCC, even after adjusting for key confounders such as age, gender, smoking, and alcohol consumption. These results reinforce the multifactorial etiology of OSCC, with a dominant contribution from areca nut–based chewing practices.

The strongest association was observed for betel quid use containing areca nut and tobacco (AOR = 4.15), followed by betel nut chewing alone (AOR = 3.42). This dose-dependent pattern is consistent with the established carcinogenic role of areca nut, particularly when combined with tobacco. Similar findings have been reported in Indian and South Asian populations, where combined exposure significantly elevates oral cancer risk due to synergistic carcinogenic mechanisms involving arecoline-induced fibroblast proliferation and tobacco-derived nitrosamines [15,16]. The observed association with prolonged chewing duration (>10 years) further supports a cumulative exposure effect, which aligns with the chronic carcinogenic process described in epidemiological studies of oral cancer progression [17].

Smoking was also independently associated with OSCC in the present study (AOR = 1.88), although the magnitude of effect was lower compared to chewing-related exposures. This finding is consistent with existing literature indicating that smoking acts as a co-factor rather than the primary driver in populations with high prevalence of smokeless tobacco and areca nut use [18]. Alcohol consumption, although showing an increased odds ratio, was not statistically significant in this study, suggesting a weaker independent effect in this population. This may reflect regional consumption patterns or potential confounding by stronger exposures such as betel quid use.

Age and gender were also significant predictors of OSCC. Increasing age was associated with higher odds of disease, reflecting cumulative exposure to carcinogens over time and age-related reduction in DNA repair capacity. Male predominance in OSCC risk observed in this study is consistent with global and regional cancer burden patterns, which are largely attributed to higher prevalence of tobacco and chewing habits among men [19,20].

The present findings are consistent with epidemiological evidence from India and South Asia, where oral squamous cell carcinoma (OSCC) remains highly prevalent and is strongly associated with smokeless tobacco and areca nut use [21,22]. Oral cancer in the region continues to occur in epidemic proportions, largely driven by betel quid chewing practices, while smokeless tobacco has been identified as a major public health burden with well-established carcinogenic potential [15,16]. Global evidence further supports a significant association between smokeless tobacco use and increased risk of oral cavity cancer, with some populations demonstrating stronger effects among females [18].

The role of lifestyle and behavioral risk factors identified in this study is further supported by systematic reviews and cancer burden analyses, which consistently highlight tobacco use, alcohol consumption, and betel nut chewing as major contributors to oral cancer development. Modifiable high-risk behaviors remain the most significant determinants of disease occurrence, while increasing cancer burden has been reported in populations with persistent exposure to these risk factors, particularly in India [23-25]. Additionally, global cancer trend analyses confirm a sustained burden of oral and pharyngeal cancers, especially in low- and middle-income countries, where chewing habits and other behavioral risk factors remain highly prevalent [19,20].

The strength of this study lies in its histopathologically confirmed cases, structured exposure assessment, and multivariable adjustment for key confounders. However, as a hospital-based case–control study, potential limitations include recall bias and selection bias, as well as inability to establish temporal causality. Despite these limitations, the consistency of findings with existing literature strengthens the validity of the observed associations.

CONCLUSION

This research confirms that betel nut chewing, especially when combined with tobacco, constitutes a significant independent risk factor for oral squamous cell carcinoma (OSCC). The results highlight the critical necessity for targeted public health initiatives, enhanced regulation of smokeless tobacco products, and community-based awareness programs aimed at decreasing areca nut consumption and alleviating the increasing prevalence of oral cancer in South Asia.

FUNDING

This research received no specific funding from any public, commercial, or not-for-profit funding agencies.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this study.

REFERENCES

1. Warnakulasuriya S, Chen THH. Areca nut and oral cancer: evidence from studies conducted in humans. J Dent Res. 2022;101(10):1139–46. doi:10.1177/00220345221092751.
2. Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, et al. Oral squamous cell carcinomas: state of the field and emerging directions. Int J Oral Sci. 2023;15(1):44. doi:10.1038/s41368-023-00249-w.
3. Bouvard V, Nethan ST, Singh D, Warnakulasuriya S, Mehrotra R, Chaturvedi AK, et al. IARC perspective on oral cancer prevention. N Engl J Med. 2022;387(21):1999–2005. doi:10.1056/nejmsr2210097.
4. Wang M, Chang X, Ni P, Yu J, Wang X, Sun H. Correlation of betel quid with oral cancer from 1998 to 2017. Chin Med J (Engl). 2018;131(16):1975–82. doi:10.4103/0366-6999.238140.
5. Lin NC, Hsien SI, Hsu J, Chen MY. Impact on patients with oral squamous cell carcinoma in different anatomical subsites: a single-center study in Taiwan. Sci Rep. 2021;11:15446. doi:10.1038/s41598-021-95007-5.
6. Jayasooriya PR, Pitakotuwage TN, Mendis BRRN, Lombardi T. Descriptive study of 896 oral squamous cell carcinomas from the only university-based oral pathology diagnostic service in Sri Lanka. BMC Oral Health. 2016;16:1. doi:10.1186/s12903-015-0139-y.
7. Gocol H, Zeng JH, Chang S, Koh BY, Nguyen H, Cirillo N. A critical interpretive synthesis of the role of arecoline in oral carcinogenesis: is the local cholinergic axis a missing link in disease pathophysiology? Pharmaceuticals (Basel). 2023;16(12):1684. doi:10.3390/ph16121684.
8. Chen T, Wu C, Ko J, Yang T, Lou P, Wang C, et al. Clinical characteristics and treatment outcome of oropharyngeal squamous cell carcinoma in an endemic betel quid region. Sci Rep. 2020;10:526. doi:10.1038/s41598-019-57177-1.
9. Yu N, Cai W, Zhang C, Cai Q, Zhang Z, Hu Y, et al. The multistep progression of areca nut-induced oral cancer: a mechanistic roadmap from pathogenesis to precision therapy. Life Med. 2026. doi:10.1093/lifemedi/lnag011.
10. Dong L, Xue L, Cheng W, Tang J, Ran J, Li Y. Comprehensive survival analysis of oral squamous cell carcinoma patients undergoing initial radical surgery. BMC Oral Health. 2024;24:919. doi:10.1186/s12903-024-04690-z.
11. Manikandan M, Rao AKDM, Arunkumar G, Manickavasagam M, Seenivasagam RK, Rajaraman R, et al. Oral squamous cell carcinoma: microRNA expression profiling and integrative analyses for elucidation of tumourigenesis mechanism. Mol Cancer. 2016;15:28. doi:10.1186/s12943-016-0512-8.
12. Meng S, Lv A, Li N, Ding X. Global, regional, and national burden of lip and oral cavity cancer and projections to 2036. BMC Cancer. 2025;25:1573. doi:10.1186/s12885-025-14995-z.
13. Rajakumar HK, Sathyabal VC, Jabarulla KN, Balamurugesan P. Development and validation of betel-year: a clinical tool for quantifying exposure to betel quid chewing. BMC Cancer. 2024;24:930. doi:10.1186/s12885-024-12685-w.
14. Li Z, Fu Y, Hu Y, Zhu Y, Hu L, Shi C, et al. Low-dose arecoline regulates distinct core signaling pathways in oral submucous fibrosis and oral squamous cell carcinoma. BMC Oral Health. 2023;23:171. doi:10.1186/s12903-023-02887-2.
15. Gupta B, Ariyawardana A, Johnson NW. Oral cancer in India continues in epidemic proportions: Evidence base and policy initiatives. Int Dent J 2013;63:12-25.
16. Gupta PC, Arora M, Sinha D, Asma S, Parascondola M. Smokeless Tobacco and Public Health in India. New Delhi: Ministry of Health and Family Welfare, Government of India; 2016.

17. Acharya S, Tayaar AS. Analysis of clinical and histopathological profiles of oral squamous cell carcinoma in young Indian adults: A retrospective study. J Dent Sci 2012;7:224-30.
18. Mu G, Wang J, Liu Z, Zhang H, Zhou S, Xiang Q, et al. Association between smokeless tobacco use and oral cavity cancer risk in women compared with men: A systematic review and meta-analysis. BMC Cancer 2021;21:960.
19. Huang J, Chan SC, Ko S, Lok V, Zhang L, Lin X, et al. Disease burden, risk factors, and trends of lip, oral cavity, pharyngeal cancers: A global analysis. Cancer Med 2023;12:18153-64.
20. Ghantous Y, Abu Elnaaj I. Global incidence and risk factors of oral cancer. Harefuah 2017;156:645-9.
21. Babu C, Pereira T, Shetty S, Shrikant GS, Anjali AK, Vidhale RG. Epidemiological trends of oral squamous cell carcinoma-an institutional study. Muller J Med Sci Res 2021;12:1-5.
22. Ray CS, Gupta PC. Oral cancer in India. Oral Dis 2025;31:1439-54.
23. Irani S. New insights into oral cancer-risk factors and prevention: A review of literature. Int J Prev Med 2020;11:202.
24. Jena D, Swain PK, Gandhi NC, Guthi VR, Sree Sudha TY, Priyadharshini P, et al. Cancer burden and trends across India (1990–2021): Insights from the global burden of disease study. Evidence 2024; 2:3-4.
25. Chintapally N, Nuwayhid M, Arroju V, Muddu VK, Gao P, Reddy BY, et al. State of cancer care in India and opportunities for innovation. Future Oncol 2023;19:2593-606.