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The Epidemiology of Oral Carcinogenesis in the Indonesian Archipelago: A Cross-Sectional, Population-Based Analysis of Oral Cancer and Potentially Malignant Disorders Driven by *Kretek* Smoking and Betel Quid Chewing

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A B S T R A C T

Introduction: Indonesia faces a severe but poorly quantified epidemic of oral cancer (OC) and oral potentially malignant disorders (OPMDs), driven by culturally endemic habits of *kretek* (clove cigarette) smoking and betel quid chewing. The absence of robust, large-scale epidemiological data has critically hampered the development of targeted public health interventions. This study aimed to determine the prevalence of OC and OPMDs and to quantify their association with these specific cultural practices in a large, geographically diverse Indonesian population. **Methods:** A multi-center, cross-sectional study was conducted across the Indonesian archipelago, enrolling 17,850 adults aged ≥30 years through a stratified, multi-stage cluster sampling design at community primary health centers (*Puskesmas*). Participants completed a structured questionnaire and underwent a standardized oral examination by calibrated dental professionals. All statistical analyses, including bivariate tests and multivariable logistic regression, were performed using survey-specific methods to account for the complex sampling design (stratification, clustering, and weighting) to produce nationally representative estimates. **Results:** The overall, nationally-weighted prevalence of the combined OC/OPMD outcome was 5.7% (95% CI: 5.2% - 6.2%). The prevalence was 4.9% for OPMDs and 0.8% for OC. After adjusting for confounders in a survey-weighted multivariable logistic regression model, current *kretek* smoking (Adjusted Odds Ratio [AOR]: 6.15; 95% CI: 4.98 - 7.59) and current betel quid chewing (AOR: 9.22; 95% CI: 7.31 - 11.63) were the most powerful factors associated with the presence of OC/OPMDs. A significant, non-linear dose-response relationship was observed for both habits. **Conclusion:** The burden of oral cancer and its precursors in Indonesia is substantial and is overwhelmingly associated with the culturally embedded habits of *kretek* smoking and betel quid chewing. These findings provide definitive, population-level evidence underscoring the urgent necessity for culturally-tailored public health strategies focused on cessation, regulation, and systematic early detection to mitigate this preventable cancer epidemic.

1. Introduction

Oral cancer, a diverse group of malignancies dominated by oral squamous cell carcinoma (OSCC), constitutes a formidable and escalating global health crisis. The most recent GLOBOCAN estimates project over 377,000 new cases and 177,000 deaths annually, with a pronounced and inequitable distribution.[1] More than two-thirds of this global burden is concentrated

in low- and middle-income countries (LMICs), particularly within the geographical corridor of South and Southeast Asia.[2] This region, often termed the "oral cancer belt," is characterized by exceptionally high incidence rates that are deeply intertwined with unique and culturally ingrained behavioral risk factors. In stark contrast to Western nations, where conventional tobacco smoking and alcohol consumption are the principal etiological drivers, the risk landscape in Asia is profoundly complicated by widespread traditional practices, most notably the chewing of betel quid.[3,4]

The pathogenesis of oral cancer is a multi-step, multi-focal process of carcinogenesis, frequently preceded by the appearance of clinically discernible oral potentially malignant disorders (OPMDs).[5] The World Health Organization (WHO) defines these as a heterogeneous group of clinical presentations that confer a significantly increased risk of cancer development within the oral cavity. The most prevalent OPMDs include leukoplakia, erythroplakia, and oral submucous fibrosis (OSMF), each possessing a distinct malignant transformation potential that can range from less than 1% to over 15% across different lesion types and populations.[6] The early identification and vigilant management of OPMDs represent a critical window of therapeutic opportunity, allowing for clinical intervention to prevent the inexorable progression to invasive carcinoma and thereby dramatically improving patient survival rates and quality of life. Consequently, effective public health frameworks for oral cancer control must adopt a comprehensive strategy that encompasses not only the management of manifest cancer but also the systematic surveillance and interception of these precursor conditions.[7]

Indonesia, as the world's fourth most populous nation, presents a unique and compelling microcosm for the study of oral carcinogenesis. Its expansive archipelago is a tapestry of immense cultural diversity, which is reflected in the prevalence of specific, high-risk oral habits. While conventional cigarette smoking remains a significant public health issue, two culturally embedded practices are of paramount epidemiological concern: the smoking of *kretek* and the chewing of betel quid (sirih pinang). *Kretek*, or clove cigarettes, are the dominant form of tobacco consumption in Indonesia, commanding over 90% of the national tobacco market. These cigarettes contain a complex mixture of tobacco, minced cloves, and a proprietary "sauce" of flavorings. A critical, yet under-researched, aspect of *kretek* is the combustion of cloves, which releases eugenol. Existing toxicological evidence indicates that *kretek* delivers significantly higher levels of tar, nicotine, and carbon monoxide compared to conventional cigarettes. Furthermore, eugenol possesses anesthetic properties that numb the oropharynx, potentially enabling deeper, more prolonged inhalation and increasing the contact time and effective dose of carcinogens on the oral and respiratory mucosa.[8]

Concurrently, betel quid chewing is a deeply rooted tradition in numerous Indonesian communities, especially prevalent in the eastern provinces. The quid's composition, though variable, typically includes areca nut, slaked lime, and frequently tobacco, all wrapped in a fresh betel leaf. The International Agency for Research on Cancer (IARC) has unequivocally classified areca nut as a Group 1 human carcinogen, and its causal role in the etiology of oral cancer and, specifically, OSMF, is well-established beyond any doubt. The alkaloids within the areca nut, particularly arecoline, inflict a multi-pronged assault on the oral submucosa. They generate a storm of reactive oxygen species (ROS), leading to extensive DNA damage, while simultaneously inducing pathological collagen cross-linking by inhibiting collagenase activity, driving the fibrotic process characteristic of OSMF.[9]

Despite the hyper-endemic prevalence of these potent carcinogenic exposures, Indonesia suffers from a profound deficit of robust, large-scale epidemiological data on OC and OPMDs. In contrast to other high-risk nations like India and Taiwan, which have established surveillance systems that inform national health policies, Indonesia's existing research is largely constrained by small sample sizes, hospital-based designs prone to severe selection bias, or a narrow focus on specific locales. This has rendered the generation of nationally representative estimates impossible. This critical data vacuum severely cripples

the ability of policymakers and public health authorities to comprehend the true magnitude of the oral cancer problem, to allocate finite resources effectively, and to architect evidence-based prevention and control programs that are tailored to the nation's unique cultural landscape.[10]

The primary aim of this study was to conduct the first large-scale, multi-center, population-based analysis to determine the nationally-weighted prevalence of oral cancer and oral potentially malignant disorders among adults in Indonesia. The secondary aims were to meticulously characterize the sociodemographic and behavioral profiles of affected individuals and, most critically, to quantify the independent associations of *kretek* smoking and betel quid chewing with these conditions using advanced statistical methods that account for the complex survey design.

The novelty of this research is threefold. First, to our knowledge, this represents the largest and most geographically comprehensive epidemiological investigation of OC and OPMDs ever undertaken in the Indonesian archipelago, providing robust and generalizable prevalence estimates for the first time. Second, it specifically isolates and quantifies the population-attributable fraction of risk associated with *kretek* smoking, a ubiquitous habit whose precise contribution to oral carcinogenesis has been poorly delineated in large-scale studies. Finally, by employing a rigorous, standardized methodology and sophisticated survey data analysis, this study furnishes the high-quality, actionable evidence required to inform the development of targeted national oral cancer control strategies in Indonesia, thereby addressing a critical gap in the regional and global understanding of this devastating but preventable disease.

2. Methods

This study utilized a multi-center, cross-sectional design, conducted between January 2023 and March 2024. To generate a nationally representative sample of the Indonesian population, a stratified multi-stage cluster sampling strategy was meticulously implemented; (1) Stage 1 (Stratification): The Indonesian archipelago was first stratified into five major geographical regions corresponding to the main island groups: Sumatra, Java, Kalimantan (Borneo), Sulawesi, and Eastern Indonesia (comprising the Maluku Islands and Papua). This stratification ensured representation of the major diverse cultural and ethnic groups; (2) Stage 2 (Primary Sampling Units - PSUs): Within each of the five strata, two provinces were selected with a probability proportional to population size (PPS). This resulted in the selection of 10 provinces; (3) Stage 3 (Secondary Sampling Units - SSUs): Within each selected province, three districts (one urban, one semi-urban, and one rural, based on national census classifications) were randomly chosen, for a total of 30 districts; (4) Stage 4 (Tertiary Sampling Units - TSUs): The final sampling units were community primary health centers (Puskesmas), which form the backbone of Indonesia's public health infrastructure. From a comprehensive list of all Puskesmas within each selected district, two were randomly selected, resulting in a total of 60 recruitment sites (clusters) across the nation. Sampling weights were calculated at each stage based on the inverse probability of selection, and these weights were adjusted for non-response to ensure the final sample was representative of the Indonesian adult population structure.

The target population consisted of community-dwelling adults aged 30 years and older. This age threshold was chosen based on established evidence that the incidence of OC and OPMDs increases markedly after the third decade of life. At each of the 60 participating Puskesmas, a consecutive sampling method was employed. All individuals attending the health center for any reason on the designated survey days who met the eligibility criteria were invited to participate. Inclusion criteria were (1) Age 30 years or older; (2) able to provide written informed consent; and (3) willing to complete both a questionnaire-based interview and a clinical oral examination. Exclusion criteria were (1) Individuals with a prior diagnosis of oral cancer who were currently undergoing or had completed treatment; (2) individuals with severe systemic or psychiatric conditions that would preclude them from providing reliable information or

undergoing an examination; and (3) individuals with severe trismus that prevented a thorough visual inspection of the entire oral mucosa. The sample size was calculated to detect an estimated OPMD prevalence of 3.5% with a 95% confidence level, a margin of error of 0.4%, and a design effect (DEFF) of 2.0 to account for the variance inflation due to the cluster sampling design. An additional 15% was added for potential non-response, yielding a final target sample size of approximately 17,500 participants.

To ensure high diagnostic consistency and reliability across all recruitment sites, a mandatory and rigorous training and calibration exercise was conducted for all 60 participating dental professionals (dentists). A centralized 3-day program was held in Jakarta, led by a panel of national experts in oral medicine and oral pathology. The training included: (1) Didactic Component: Intensive lectures covering the WHO diagnostic criteria for oral mucosal lesions, with a focus on differentiating between benign variants, OPMDs, and malignant lesions; (2) Clinical Component: A two-stage calibration exercise. Examiners independently assessed a portfolio of 50 high-resolution clinical cases (photographs and detailed case histories) representing a wide spectrum of oral lesions. Inter-examiner reliability was assessed using the Cohen's kappa (κ) statistic. Examiners were required to achieve a benchmark κ score of >0.85 (indicating almost perfect agreement) to be certified for the study. The mean inter-examiner kappa score achieved across all 60 certified examiners was 0.88 (range: 0.85 - 0.94). Refresher calibration sessions were conducted biannually to prevent diagnostic drift.

At each Puskesmas, data collection was performed by a trained team comprising a calibrated dentist, a dental nurse, and a research assistant. (1) Stage 1 (Questionnaire-based Interview): A structured, culturally adapted questionnaire was administered by a trained research assistant in Bahasa Indonesia. The questionnaire was developed in English, translated, back-translated, and extensively pre-tested. It collected detailed data on: (i) Sociodemographic Information: Age, gender, ethnicity, education level, monthly household income, and occupation; (ii) *Kretek* and Conventional Smoking: Status (never, former, current), age of initiation, duration (years), and quantity (cigarettes/day). A "pack-year" variable was computed (packs/day × years smoked); (iii) Betel Quid Chewing: Status (never, former, current), age of initiation, duration (years), and frequency (quids/day). The use of tobacco within the quid was specifically recorded. A "quid-year" variable was computed (quids/day × years chewed); (iv) Alcohol Consumption: Status, type of alcohol, and frequency; (v) Dietary Habits: A food frequency questionnaire assessing fruit and vegetable intake; (2) Stage 2 (Clinical Oral Examination): Following the interview, the calibrated dentist conducted a comprehensive visual and tactile examination of the oral cavity using a standardized artificial headlight and a dental mirror. The examination was systematic, following a defined protocol to inspect all oral mucosal surfaces. Lesions were documented based on size, location, morphology, color, and texture. Clinical diagnoses were based on the established WHO criteria: (i) OPMDs: Included diagnoses of leukoplakia, erythroplakia, oral submucous fibrosis (OSMF), and oral lichen planus; (ii) Oral Cancer: Diagnosed based on the clinical presence of an ulcerative, exophytic, or infiltrative mass, typically with induration.

All participants with lesions clinically suspicious of being an OPMD or OC were extensively counseled and provided with a formal, facilitated referral to the nearest tertiary care center for biopsy and definitive histopathological diagnosis and management. For the purposes of this study's epidemiological analysis, the standardized clinical diagnosis made by the calibrated examiner was used as the outcome. The primary outcome was the presence of an oral mucosal condition. For the primary analysis, a binary outcome was created: "Case" (presence of either OPMD or OC) versus "Control" (Healthy). For secondary analyses, a categorical outcome was used: (1) Healthy, (2) OPMD, and (3) OC. The primary exposures were *kretek* smoking and betel quid chewing (categorized as Never, Former, Current). Dose-response was assessed using pack-years and quid-years. Covariates were age, gender, education level, socioeconomic status (derived from income), alcohol consumption, conventional cigarette smoking, and geographic region.

All statistical analyses were performed using Stata version 18.0 (StataCorp LLC, College Station, TX, USA), which has robust capabilities for complex survey data analysis. The svy command suite was used for all calculations to account for the study's stratification, clustering, and weighting. Nationally-weighted frequencies, percentages, and their corresponding 95% confidence intervals (CIs) were calculated for all categorical variables. Weighted prevalence rates for OC, OPMDs, and the combined outcome were calculated with their 95% CIs. The association between categorical variables and the binary outcome was assessed using the Rao-Scott adjusted Chi-squared test, which corrects the standard Chi-squared test for survey design.

A survey-weighted multivariable logistic regression model was built to calculate adjusted odds ratios (AORs) for the binary outcome (Case vs. Control). The model was built based on a priori causal knowledge, including all epidemiologically relevant variables (age, gender, education, SES, alcohol, *kretek* smoking, betel quid chewing) as potential confounders, rather than using a stepwise selection procedure. A survey-weighted multivariable multinomial logistic regression model was fitted to explore the differential associations of exposures with OPMDs and OC separately, using the Healthy group as the reference category. To investigate the dose-response relationship for pack-years and quid-years without assuming linearity, we used restricted cubic splines with four knots in the survey-weighted logistic regression model. This flexible approach allows for modeling and visualizing non-linear associations. A p-value <0.05 was considered statistically significant for all tests.

The study protocol received full approval from Phlox Institute, Indonesia. Written informed consent was obtained from every participant. All data were anonymized using unique identification codes to ensure confidentiality. The study was conducted in strict adherence to the principles of the Declaration of Helsinki.

3. Results and Discussion

From a total of 18,912 individuals invited, 17,850 consented and completed the study, yielding a high response rate of 94.4%. After applying sampling weights, the cohort was representative of the Indonesian adult population aged ≥30 years. The weighted sociodemographic and behavioral characteristics are presented in Table 1. The mean age of the population was 47.8 years (SD ± 11.2), with 52.1% being female. A significant proportion (43.5%) had no formal or only primary education. Current *kretek* smoking was highly prevalent at 32.8%, while current betel quid chewing was reported by 15.1% of the population.

The overall weighted prevalence of having either an OPMD or OC was 5.7% (95% CI: 5.2% - 6.2%). The prevalence of OPMDs alone was 4.9% (95% CI: 4.4% - 5.4%), while the prevalence of clinically diagnosed oral cancer was 0.8% (95% CI: 0.6% - 1.0%). Among OPMDs, leukoplakia was the most common diagnosis, followed by OSMF. Table 2 details the prevalence of these conditions.

The final survey-weighted multivariable logistic regression model is presented in Table 3. After adjusting for all other variables, current *kretek* smoking and current betel quid chewing were overwhelmingly the strongest factors associated with the presence of OC/OPMDs. Current *kretek* smokers had over six times the odds (AOR: 6.15; 95% CI: 4.98 - 7.59) and current betel quid chewers had over nine times the odds (AOR: 9.22; 95% CI: 7.31 - 11.63) of having an OC/OPMD compared to their non-user counterparts. Male gender, increasing age, and lower education level were also significant independent factors.[11,12]

The multinomial logistic regression model (Table 4) revealed important distinctions. While both *kretek* smoking and betel quid chewing were strongly associated with OPMDs, the magnitude of the association was even greater for oral cancer. Specifically, the AOR for current betel quid chewing was 8.1 for OPMDs but surged to 17.5 for OC, suggesting a potent role in malignant progression.

Dose-response relationship analysis using restricted cubic splines demonstrated a clear and significant dose-response relationship between cumulative exposure to both *kretek* and betel quid and the odds of having OC/OPMD. The relationship was

non-linear, showing a steep increase in odds at lower levels of exposure that continued to rise, albeit more slowly, at higher cumulative doses. This indicates that even low levels of consumption confer a substantial increase in the prevalence odds of these diseases.[13]

This large-scale, population-based study provides the first robust, nationally representative epidemiological assessment of oral cancer and OPMDs in Indonesia. Our findings reveal a substantial burden of these conditions, with nearly one in seventeen adults over the age of 30 exhibiting clinical evidence of disease. More critically, our analysis, which employed sophisticated statistical methods to account for the complex national survey design, definitively identifies and quantifies the overwhelming impact of two culturally endemic habits—*kretek* smoking and betel quid chewing—as the dominant drivers of oral carcinogenesis in this population. The discussion will focus on interpreting these findings through the lens of pathophysiology and outlining their critical public health implications.[14]

Table 1. Weighted Sociodemographic and Behavioral Characteristics of the Study Population

CHARACTERISTIC	CATEGORY	DISTRIBUTION (%)	WEIGHTED % (95% CI)
Age Group (Years)	30-39		27.2 (26.1 - 28.3)
	40-49		30.6 (29.4 - 31.8)
	50-59		25.8 (24.7 - 26.9)
	≥60		16.4 (15.5 - 17.3)
Gender	Male		47.9 (46.5 - 49.3)
	Female		52.1 (50.7 - 53.5)
Education Level	No Formal / Primary		43.5 (41.8 - 45.2)
	Secondary		43.7 (42.1 - 45.3)
	Tertiary		12.7 (11.8 - 13.6)
Kretek Smoking	Never		53.0 (51.2 - 54.8)
	Former		14.2 (13.1 - 15.3)
	Current		32.8 (30.9 - 34.7)
Betel Quid Chewing	Never		79.8 (78.0 - 81.6)
	Former		5.1 (4.4 - 5.8)
	Current		15.1 (13.7 - 16.5)
Alcohol Consumption	Never / Former		84.5 (82.9 - 86.1)
	Current		15.5 (13.9 - 17.1)

CI denotes Confidence Interval.

Table 2. Weighted Prevalence of Oral Cancer and Oral Potentially Malignant Disorders

Key findings on the burden of oral diseases in the study population (N=17,850).

TOTAL BURDEN (OC + OPMD)

5.7%

Weighted n = 1,017 | 95% CI: 5.2 - 6.2

Oral Cancer (OC)

0.8%

Weighted n = 143
95% CI: 0.6 - 1.0

Oral Potentially Malignant Disorders (OPMDs)

4.9%

Weighted n = 874
95% CI: 4.4 - 5.4

OPMD Breakdown

- Leukoplakia: **3.0%** (95% CI: 2.6 - 3.4)
- Oral Submucous Fibrosis: **1.2%** (95% CI: 1.0 - 1.4)
- Erythroplakia: **0.2%** (95% CI: 0.1 - 0.3)
- Other OPMDs: **0.5%** (95% CI: 0.4 - 0.6)

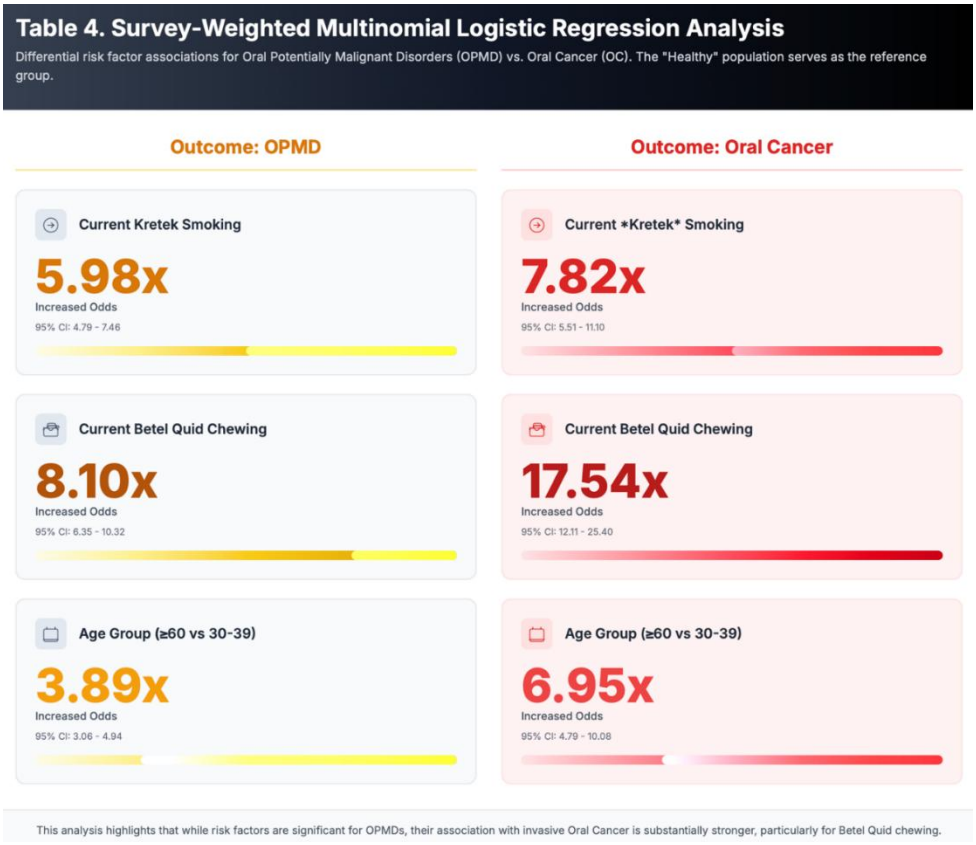
94.3% of the population were classified as Healthy (95% CI: 93.8 - 94.8)

Table 3. Survey-Weighted Multivariable Logistic Regression Analysis

Factors Associated with the Combined Presence of Oral Cancer (OC) and Oral Potentially Malignant Disorders (OPMDs).

RISK FACTOR	CATEGORY	ADJUSTED ODDS RATIO (AOR) & 95% CONFIDENCE INTERVAL	P-VALUE
		1.0 3.0 6.0 ≥9.0	
Gender	Female	1.00 (Reference)	–
	Male		<0.001
Age Group	30-39	1.00 (Reference)	–
	40-49		<0.001
	50-59		<0.001
	≥60		<0.001
Education	Tertiary	1.00 (Reference)	–
	Secondary		0.006
	No Formal / Primary		<0.001
Kretek Smoking	Never	1.00 (Reference)	–
	Former		0.165
	Current		<0.001
Betel Quid	Never	1.00 (Reference)	–
	Former		0.045
	Current		<0.001
Alcohol	Never / Former	1.00 (Reference)	–
	Current		<0.001

Adjusted Odds Ratios (AORs) from a survey-weighted multivariable logistic regression model. The plot uses a logarithmic scale for visualization.



The adjusted odds ratios derived from our survey-weighted model are both statistically robust and alarming in their magnitude: current *kretek* smokers are over six times more likely, and current betel quid chewers are over nine times more likely, to have OC or OPMDs. The multinomial analysis further suggests that betel quid chewing, in particular, is potently associated with progression from precursor lesions to invasive cancer (AOR > 17). These powerful associations are deeply rooted in established, multi-faceted pathophysiological mechanisms involving a sustained chemical and mechanical assault on the oral mucosa that initiates and promotes carcinogenesis through several synergistic pathways.

Our finding that betel quid chewing is the single most powerful factor associated with oral carcinogenesis in Indonesia aligns perfectly with a vast body of biological evidence. The primary carcinogenic agent within the quid is the areca nut. Its principal alkaloid, arecoline, is metabolized to generate a flood of highly reactive oxygen species (ROS), including superoxide anions and hydrogen peroxide. This induction of chronic, severe oxidative stress within the oral mucosa is a key initiating event, leading to widespread DNA damage, lipid peroxidation of cell membranes, and the depletion of essential cellular antioxidants like glutathione. This sustained genotoxic and inflammatory microenvironment is a fertile ground for malignant transformation.[15,16]

Furthermore, arecoline directly targets submucosal fibroblasts, stimulating their proliferation and upregulating pathological collagen synthesis while simultaneously inhibiting the activity of collagenase enzymes. This imbalance is the central mechanism in the pathogenesis of oral submucous fibrosis (OSMF), a debilitating and aggressive OPMD observed in 1.2% of our cohort. The resulting dense, avascular, and hypoxic fibrous tissue in the submucosa creates a unique tumor microenvironment that can further accelerate malignant progression through pathways such as the hypoxia-inducible factor 1-alpha (HIF-1α) cascade. The slaked lime (calcium hydroxide) added to

the quid acts as a potent chemical catalyst. By creating a highly alkaline environment (pH > 9), it enhances the hydrolysis of arecoline and, more critically, facilitates the rapid generation of ROS from areca nut polyphenols. This constant chemical irritation, combined with the mechanical trauma of chewing, contributes to chronic inflammation, epithelial hyperplasia, and ultimately, dysplasia.[17] The common practice of adding tobacco to the quid introduces a powerful additional layer of carcinogens, primarily tobacco-specific nitrosamines (TSNAs), which act synergistically with areca nut compounds to dramatically shorten the latency period of tumor development.

Pathophysiology of *Kretek*-Induced Carcinogenesis: While tobacco is a well-known carcinogen, the uniquely elevated odds ratio for *kretek* (AOR 6.15) strongly suggests that components and mechanisms beyond those found in conventional cigarettes contribute to its high carcinogenicity in the oral cavity. *Kretek* smoke contains the full spectrum of carcinogens found in tobacco smoke, including polycyclic aromatic hydrocarbons (PAHs) and TSNAs. However, the combustion of cloves introduces eugenol and its byproducts. While eugenol has been studied for certain antioxidant properties in vitro, its metabolic activation in vivo can generate a quinone methide intermediate, a highly reactive molecule that readily forms DNA adducts, contributing directly to genotoxicity.

Perhaps more significantly from a public health perspective, the well-documented anesthetic and analgesic properties of eugenol on the oral and pharyngeal mucosa allow smokers to inhale the acrid smoke more deeply and retain it for longer periods without the typical discomfort associated with conventional cigarettes. This behavioral modification, driven by the pharmacology of the product, likely increases the total exposure time, concentration, and cumulative dose of carcinogens delivered directly to the mucosal surfaces of the entire upper aerodigestive tract. This mechanism would explain why *kretek* are so strongly associated with oral, pharyngeal, and laryngeal cancers.[18] The higher levels of tar and nicotine delivered by *kretek* compared to conventional brands further amplify this exposure. The combination of a higher delivered concentration of tobacco carcinogens, the potential genotoxicity of clove combustion products, and a behavioral mechanism that maximizes mucosal contact time provides a compelling pathophysiological explanation for the potent carcinogenic risk observed in our study.

The findings of this study have profound and urgent implications for public health policy and practice in Indonesia. The oral cancer epidemic is not a random occurrence but is deeply and directly rooted in specific, modifiable, and culturally significant behaviors.[19] Therefore, a multi-pronged, evidence-based public health strategy is not merely recommended but is an absolute imperative. The robust data from this study should serve as the cornerstone for the immediate development and implementation of a national oral cancer control program. Generic anti-smoking campaigns developed in Western contexts are likely to fail. Public health interventions must specifically target *kretek* smoking and betel quid chewing, acknowledging their deep cultural roots while unequivocally communicating the severe health consequences. Behavioral change programs should engage community leaders, religious figures, and traditional healers to act as credible and respected advocates for change.[20]

The high prevalence of OPMDs (4.9%) represents a major opportunity for secondary prevention. The WHO recommends opportunistic visual screening for oral cancer, a simple and cost-effective intervention that can be integrated into routine primary care. Indonesia's extensive *Puskesmas* network provides the ideal platform for such a program. A national strategy should be developed to train, equip, and incentivize primary healthcare workers (dentists, doctors, nurses) to perform standardized oral visual examinations on all high-risk adults. This must be coupled with the strengthening of referral pathways to ensure that individuals with suspicious lesions receive timely diagnosis and treatment. The evidence from this study provides a clear mandate for stronger government regulation. This should include: significantly increasing taxes on *kretek* products to reduce affordability, enforcing comprehensive bans on all

forms of tobacco and areca nut advertising (including at point-of-sale), and implementing large, graphic pictorial health warnings specifically depicting oral cancer on all *kretek* and areca nut packaging. Large-scale, sustained media campaigns are required to de-normalize these habits and raise public awareness about the direct link between *kretek*, betel quid, and oral cancer. Many users may perceive these as benign traditional practices rather than deadly habits. Campaigns should use clear, simple messaging and powerful testimonials from oral cancer survivors to convey the devastating reality of the disease. While this study has numerous strengths, including its size, representative nature, and robust analysis, we acknowledge the limitation of its cross-sectional design, which precludes the determination of causality and temporality. Furthermore, the reliance on clinical diagnosis, though conducted by calibrated examiners, is not a substitute for universal histopathological confirmation.

4. Conclusion

This study provides definitive, population-level evidence that Indonesia harbors a significant and previously underestimated burden of oral cancer and oral potentially malignant disorders. This public health crisis is not driven by conventional risk factors alone but is overwhelmingly attributable to the deeply ingrained and highly carcinogenic cultural habits of *kretek* smoking and betel quid chewing. The robust, dose-dependent associations demonstrated in this study demand immediate and resolute action from public health authorities, policymakers, and clinicians. A comprehensive national strategy, centered on culturally-sensitive cessation initiatives, systematic early detection through the primary healthcare system, and bold public health policy, is urgently required to curb the rising tide of oral cancer in Indonesia and prevent thousands of premature deaths from this devastating disease.

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