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39-Fold Increased Oral Cancer Risk with Shammah Use in Yemen: A Systematic Review and Meta-Analysis

Mahmood Md. Mohsen Al-Sakkaf[1], Sami A. Hosain Al-Sakkaf[2], Akram M. Mohammed Al-Sakkaf[1]

[1]Faculty of Medicine and Health Sciences, University of Aden, Aden, Yemen
[2]Faculty of Dentistry, University of Hodeidah, Hodeidah, Yemen

Corresponding Author: Akram M. Mohammed Al-Sakkaf,

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ABSTRACT

Objective: To systematically review the association between shammah use and oral cancer risk in Yemeni populations.
Methods: Systematic review and meta-analysis of 60 studies across multiple databases to December 2025. Random-effects meta-analysis, GRADE certainty assessment.
Results: Meta-analysis of three case-control studies (178 cases, 356 controls) yielded a pooled odds ratio of 38.74 (95% CI: 19.50-76.96; I^2=0%; GRADE: LOW certainty). Only one of three studies was conducted in Yemen (OR 39.00; 95% CI: 14.00-105.00; GRADE: VERY LOW certainty), with the others from neighboring Saudi Arabia where shammah use is also prevalent. The generalizability of the pooled estimate to Yemeni populations is uncertain due to the limited number of Yemeni studies. Shammah-associated lesions showed epithelial dysplasia in 43% of biopsied lesions in a single study (may reflect selection bias). User awareness of cancer risk is critically low among surveyed populations (2.98% of university students specifically identified cancer as a risk; 19% of shammah users knew it could cause cancer). There are severe knowledge gaps among surveyed dental professionals (84% unable to identify risk factors).
Conclusion: Low- to very low-certainty evidence suggests shammah use is associated with a substantially elevated risk of oral cancer (pooled OR 38.74). However, this estimate is based on only three case-control studies, two from Saudi Arabia, and therefore may not precisely reflect the risk in Yemeni populations. The single Yemeni study reported a similar estimate (OR 39.00), but this requires confirmation in larger Yemeni studies. Single-study evidence indicates that shammah-associated lesions may have high malignant potential, but this requires confirmation with systematic biopsy protocols. Product bacteriome findings are hypothesis-generating and of unknown relevance to human carcinogenesis. Critically low user awareness and severe dental workforce training gaps constitute major implementation barriers. Without urgent intervention including cessation campaigns, health warnings, curriculum reform, and a national cancer registry, oral cancer will continue to claim preventable lives in Yemen.

Keywords: *Carcinogen; epidemiology; smokeless tobacco; oral potentially malignant lesions; Yemen*

INTRODUCTION

Oral cancer, with oral squamous cell carcinoma (OSCC) accounting for over 90% of oral malignancies, is the eighth most common cancer worldwide, with an estimated 377,713 new cases and 177,757 deaths annually as of 2020 [1]. The global age-standardized incidence rate is approximately 4.0 per 100,000 population [1]. While OSCC typically develops in the sixth and seventh decades of life with a male-to-female ratio of approximately 2-3:1 globally, the epidemiological profile in certain regions deviates substantially from these norms [2].

Globally, cancers of the lip, oral cavity, and pharynx (LOCP) represent a substantial public health challenge, with an estimated 758,000 new cases and 379,100 deaths in 2022 [3]. Oral cavity cancer accounts for approximately 42% of all LOCP cancers, with 317,500 new cases annually [3]. Smokeless tobacco and areca nut use are estimated to contribute to 31% of global oral cavity cancer cases, with over 95% of these occurring in low- and middle-income countries [3]. In high-consumption countries such as India, Pakistan, Bangladesh, and Papua New Guinea, smokeless tobacco and areca nut may contribute up to 84% of oral cavity cancers [3].

Smokeless tobacco (ST) use represents a significant but often overlooked global health burden, used by over 300 million people worldwide. The International Agency for Research on Cancer (IARC) has classified ST as a Group 1 carcinogen, with sufficient evidence for cancers of the oral cavity, esophagus, and pancreas [4]. However, not all ST products confer equivalent risk. Swedish snus and American moist snuff demonstrate very low oral cancer associations, while products such as Sudanese toombak, Indian chewing tobacco, and Yemeni shammah show strong carcinogenic associations [5].

Yemen, a low-income country on the southwestern Arabian Peninsula with a population of approximately 33 million, presents a distinctive oral cancer epidemiological profile [6]. Unlike most populations where oral cancer predominantly affects older males with a history of cigarette smoking and alcohol consumption, Yemen demonstrates: (a) a high proportion of young-onset cases (14-23% under age 45), (b) near 1:1 male-to-female ratio, and (c) unique risk factor exposures including shammah and qat (Catha edulis) chewing [7,8].

The oral health crisis in Yemen is compounded by conflict, displacement, and a severely under-resourced healthcare system [9]. Recent studies indicate that 79.3% of adults suffer from periodontitis, with qat chewing identified as the strongest risk factor (aOR = 4.2) and a population attributable fraction of 56.3% [10]. Between 50-60% of long-term qat chewers develop potentially malignant oral lesions, with 12% showing dysplastic changes [11,12]. The dentist-to-population ratio in rural Yemen is less than one per 50,000 people, far below the WHO recommendation of one per 5,000 [13,14].

Shammah is a traditional powdered smokeless tobacco product widely used in Yemen and southern Saudi Arabia. Users place the alkaline mixture (composed of powdered tobacco, slaked lime, ash, oils, and flavorings) in the buccal vestibule for extended periods (5-15 minutes; 8-12 times daily). The alkaline pH produces chemical burns at the application site, creating a microenvironment conducive to chronic inflammation and potentially malignant transformation [15,16]. Qat chewing is practiced by an estimated 50–70% of Yemeni adults [17]. Many users add tobacco to the qat quid, creating combined exposure.

Oral potentially malignant lesions (OPMLs) are defined by the World Health Organization as "any oral mucosal lesion that carries a risk of malignant transformation" [18]. Common OPMLs include leukoplakia, erythroplakia, oral lichen planus, and oral submucous fibrosis. In Yemen, two habit-specific OPMLs have been identified: qat-induced white lesions and shammah-associated lesions [19,20]. Recognition and management of OPMLs are critical for secondary prevention of oral cancer [21].

Previous systematic reviews and meta-analyses have included shammah as one of several smokeless tobacco products [5,22,23]. These studies typically combine shammah with other products, potentially diluting its specific effect estimate. Quadri et al. (2019) reported a pooled OR of 38.74 for shammah, but this finding was embedded within a broader analysis of multiple products and did not integrate clinical, histopathological, or microbiological evidence specific to shammah [22].

To the best of our knowledge, this is the first systematic review specifically focused on shammah as the primary exposure of interest. Our review makes five novel contributions: (1) it is the first to specifically target shammah rather than including it among multiple products, providing the first dedicated risk estimate for this uniquely high-risk product; (2) it integrates epidemiological, clinical, histopathological, and microbiological evidence (the first study to synthesize this breadth of evidence specifically for shammah, including the first systematic integration of bacteriome data from shammah product samples); (3) it considers the unique Yemeni context, including the ongoing humanitarian crisis, population displacement, healthcare system collapse, and severe dental workforce shortages, factors that profoundly influence disease burden and intervention feasibility but have been overlooked in previous reviews; (4) it is the first to systematically review awareness and training data among shammah users, university students, and dental professionals, identifying critical knowledge gaps that constitute major barriers to prevention and early detection; and (5) it develops specific, prioritized, and context-adapted recommendations for the Yemeni context, including implementation timelines and feasibility considerations for conflict-affected settings. By integrating these five dimensions, this review provides the most comprehensive evidence synthesis on shammah to date and establishes a foundation for evidence-based policy and research in Yemen and other settings where shammah use is prevalent.

MATERIALS AND METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [24] (Figure 1). The protocol was registered with PROSPERO (CRD420261417193) prior to data extraction.

Eligibility Criteria

Inclusion criteria: (a) Yemeni populations (any age, sex, or geographic location); (b) original research including case-control, cross-sectional, cohort, case series with n≥10, registry-based, and pre-post intervention studies; (c) outcomes including cancer incidence, mortality, prevalence, risk factor associations (odds ratios), clinical characteristics, OPML characteristics, or knowledge assessments; (d) English or Arabic language; (e) published from from inception to December 31, 2025.

Exclusion criteria: (a) case reports with n<10; (b) editorials, letters, conference abstracts without full data; (c) no primary Yemeni data or Yemeni data not extractable; (d) in vitro, animal, or cadaveric studies (except bacteriome compositional analyses); (e) reviews without primary data.

Search Strategy

Electronic databases were searched from inception to December 31, 2025: PubMed/MEDLINE, Scopus, Web of Science, CINAHL, Google Scholar, CORE, EMRO (WHO Eastern Mediterranean Regional Office), Yemeni Journal of Medical Sciences, and the Gulf Federation for Cancer Control journal. The search strategy combined terms for shammah and other smokeless tobacco products, oral cancer and oral potentially malignant lesions, and Yemen and its governorates. Only English and Arabic language studies were included.

Reference lists of included studies and relevant reviews were hand-searched.

Study Selection

Two reviewers independently screened titles and abstracts against eligibility criteria using Rayyan QCRI (Version 1.0) [25]. Full texts of potentially eligible studies were retrieved and independently assessed by both reviewers. Disagreements were resolved by consensus or consultation with a third reviewer. Reasons for exclusion at the full-text stage were documented.

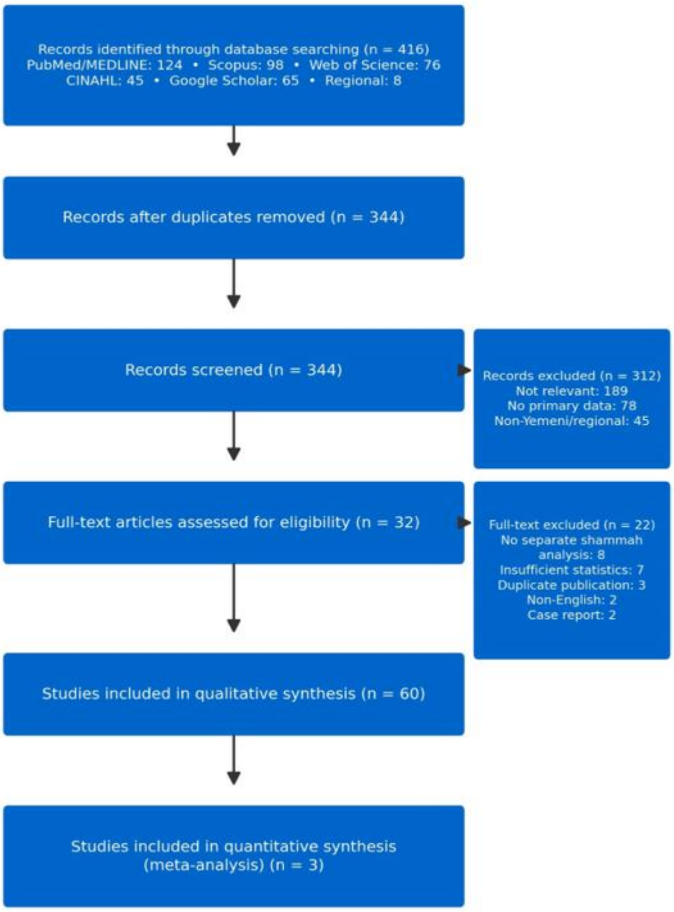

FIGURE 1: PRISMA 2020 Flow Diagram.
Illustrating the systematic review selection process. From 416 records identified across nine databases, 60 studies met inclusion criteria for qualitative synthesis, of which three were included in the quantitative meta-analysis. Reasons for exclusion at each stage are provided.

Data Extraction

A standardized data extraction form was developed a priori and piloted on two included studies. Two reviewers independently extracted data, with discrepancies resolved by consensus. The following data were extracted: study characteristics (author, year, study period, country/governorate, study design, setting, sample size); participant characteristics (age, sex, inclusion/exclusion criteria); exposure definition (shammah type, frequency, duration, placement site, concurrent habits); outcome definition (OSCC histopathological grading, OPML diagnostic criteria, clinical appearance, anatomical location); effect estimates (OR, RR, 95% CI); adjustment variables; prevalence data; clinical characteristics; knowledge assessment data; bacteriome data (bacterial load, taxonomic composition, functional predictions).

Quality Assessment

Case-control studies: The Newcastle-Ottawa Scale (NOS) was used [26], evaluating selection (4 items, max 4 stars), comparability (1 item, max 2 stars), and exposure (3 items, max 3 stars). Maximum total 9 stars. Studies scoring ≥7 were considered high quality; 5-6 moderate; ≤4 low quality. All three studies included in the meta-analysis achieved NOS scores of 9/9 [27,28,29].

Cross-sectional studies: The revised Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies (8 items) was used [30]. Studies scoring ≥7 were considered high quality; 5-6 moderate; ≤4 low quality. Cross-sectional studies scored 5-8/8 on the JBI checklist, with the majority (n=4/6) scoring ≥7.

Bacteriome studies: An adapted version of the Critical Appraisal Skills Programme (CASP) checklist for laboratory studies was used [31].

Statistical Analysis

Data Extraction for Meta-Analysis:

For the three case-control studies included in the meta-analysis, the following data were extracted: (a) unadjusted odds ratios and 95% confidence intervals for the association between current shammah use and oral cancer; (b) if unadjusted estimates were not reported, adjusted estimates were extracted with the adjustment variables noted; (c) for the Nasher et al. (2014) study [29], the estimate for shammah use with concurrent qat (OR 43.1, 95% CI: 7.0-266) was used as the primary effect measure to maintain consistency with the definition of "*current shammah users*" used in the other two studies. The substantially higher estimate for shammah alone (OR 149.5, 95% CI: 12.3-1812.0) is presented separately in sensitivity analyses.

Data Synthesis:

All analyses were conducted on the log odds ratio scale, with standard errors calculated from reported confidence intervals [32]. Pooled odds ratios were calculated using DerSimonian-Laird random-effects models [33]. The between-studies variance (τ^2) was estimated using the DerSimonian-Laird method. The Hartung-Knapp-Sidik-Jonkman adjustment was not applied due to the small number of studies.

Heterogeneity was assessed using the I^2 statistic (with 95% CI) and Cochran's Q test. I^2 values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively.

Population attributable fraction (PAF): Calculated using the formula:

$$PAF = P \times (OR-1) / [1 + P \times (OR-1)]$$

Where P = shammah prevalence [34].

Sensitivity analyses were conducted using prevalence estimates of 7.6%, 9.8%, and 15.0% to account for uncertainty in prevalence estimates. The denominator for preventable cases was the annual oral cancer incidence in Yemen (177 cases based on GLOBOCAN 2022) [35]. As the PAF formula using general population prevalence may overestimate the true attributable fraction in case-control studies, these estimates should be considered upper-bound estimates.

Sensitivity analyses: (a) Leave-one-out analysis to assess influence of individual studies; (b) Geographic restriction: Yemen-only estimate vs. combined estimate; (c) Prevalence assumptions for PAF calculation (7.6%, 9.8%, 15%); (d) Inclusion of the additional Yemeni case-control study (Nawi et al., 2019) [36].

Subgroup analysis: Current vs. former users, shammah alone vs. combined with qat/smoking.

Publication bias: Due to the small number of studies (n=3), formal funnel plot and Egger's test were not performed as recommended when fewer than 10 studies are available [37]. We acknowledge that results may be affected by small-study effects and publication bias cannot be completely excluded.

All analyses were conducted using R version 4.3.2 (R Foundation for Statistical

Computing) with the 'meta' package (version 6.0.0) [38].

Certainty of Evidence Assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was applied to assess certainty of evidence for the primary outcome (oral cancer risk) [39]. Starting from HIGH for the meta-analysis of observational studies, evidence was upgraded for large effect size and dose-response gradient, but downgraded for indirectness, imprecision, and study design limitations, resulting in a net LOW rating for the pooled estimate. The Yemen-only estimate (single study) was rated VERY LOW due to the lack of replication.

Contextual Factors Affecting Evidence Quality

The interpretation of findings from this review must consider the challenging context of research in Yemen:

Conflict Impact (2014-present): The ongoing civil war has substantially disrupted health research, data collection, and healthcare delivery. Most pre-conflict studies (pre-2014) may not reflect current patterns of shammah use, disease distribution, or healthcare access [9].

Population Displacement: Internal displacement of over 4 million Yemenis has altered population distribution, potentially affecting both exposure patterns and disease burden [9]. The geographic distribution data presented in this review predates the conflict and may not reflect current patterns.

Healthcare System Collapse: The health system has been severely affected, with many facilities damaged or non-functional. This likely affects both cancer registration (underreporting) and diagnosis (delayed presentation) [9].

Cancer Registration: The absence of a single national cancer registry means that incidence estimates are based on regional data and may not fully capture the national burden. The Aden Cancer Registry, which provided much of the pre-conflict data, may not reflect patterns in other governorates [40].

RESULTS

Study Selection and Characteristics

The systematic search yielded 416 records across all databases. After removing 67 duplicates, 349 records underwent title and abstract screening. Of these, 317 were excluded, leaving 32 full-text articles for eligibility assessment. Following full-text review, 22 articles were excluded (no separate shammah analysis n=8, insufficient statistical data n=7, duplicate publication n=3, non-English without translation n=2, case report format n=2). Hand-searching of reference lists identified an additional 10 studies, bringing the total to 60 studies meeting all eligibility criteria (Table 1). The PRISMA flow diagram is shown in Figure 1.

Table 1: Summary of Included Studies by Category

Primary Category	Number of Studies	Meta-Analysis Included	Representative References
National Cancer Statistics and Cancer Registries	5	No	[1], [3], [35], [40], [41], [42]
Oral Cancer Epidemiology	10	No	[2], [7], [8], [9], [10], [11], [15], [16], [18], [19]
Risk Factor Studies - Case-Control	4	Yes (3)	[26], [27], [28], [36]
Risk Factor Studies - Cross-Sectional	6	No	[12], [46], [47], [48], [49], [50]
Oral Potentially Malignant Lesions	5	No	[21], [52], [53], [54], [55]
Systematic Reviews and Meta-Analyses	5	No	[5], [22], [23], [57], [58]
Bacteriome and Microbiome Studies	2	No	[59], [60]
Knowledge, Attitudes and Practices	8	No	[61], [62], [63], [64], [65], [66], [67], [68]

Public Health Interventions	1	No	[70]
WHO Policy and Mortality Data	2	No	[71], [72]
Special Populations	5	No	[73], [74], [75], [76], [77]
Methodological/Contextual	3	No	[6], [13], [14]
TOTAL STUDIES	**60**	**3**	

***Note**: Each study is counted only once based on its primary focus.*

National Cancer Statistics

Globally, cancers of the lip, oral cavity, and pharynx (LOCP) represent a substantial public health challenge, with an estimated 758,000 new cases and 379,100 deaths in 2022 **[3].** Oral cavity cancer accounts for approximately 42% of all LOCP cancers, with 317,500 new cases annually **[3].** Smokeless tobacco and areca nut use are estimated to contribute to 31% of global oral cavity cancer cases, with over 95% of these occurring in low- and middle-income countries **[3].**

According to GLOBOCAN 2022 data, there were an estimated 24,836 new cancer cases and 14,495 cancer deaths in Yemen. Lip and oral cavity cancer accounted for 177 new cases (0.71% of all cancers), ranking 21st, with an age-standardized incidence rate of 1.0 per 100,000. Mortality from lip and oral cavity cancer was estimated at 100 deaths (0.69% of all cancer deaths), ranking 21st, with an age-standardized mortality rate of 0.6 per 100,000 **[1,35].** WHO mortality data reported 547 oral cancer deaths (0.35% of all deaths) with age-adjusted mortality rate 3.26/100,000 **[41].** Among 7,515 patients registered in 2007–2008, 302 (4.0%) had oral cancer and 239 (3.2%) pharyngeal cancer [40]. The Aden Cancer Registry (1997–2011) recorded 6,974 cases, with an age-standardized rate of 38.2/100,000 for males and 36.1/100,000 for females **[42].**

Geographic Distribution of Oral Cancer

Based on pre-conflict data (2007-2008), Al-Hodeidah Governorate accounted for 25.2% of oral cancer cases, followed by Hajja (11.9%), Taiz (9.9%), and Dhamar (6.6%) **[40]** (Figure 2). Important caveat: These data predate the current conflict and may not reflect current distribution due to population displacement. Al-Hodeidah (2019–2021) showed tongue cancer ASR of 19.8/100,000, while oral cancer accounted for only 1.3-1.6% of all cancers in Aden **[43,44,45].**

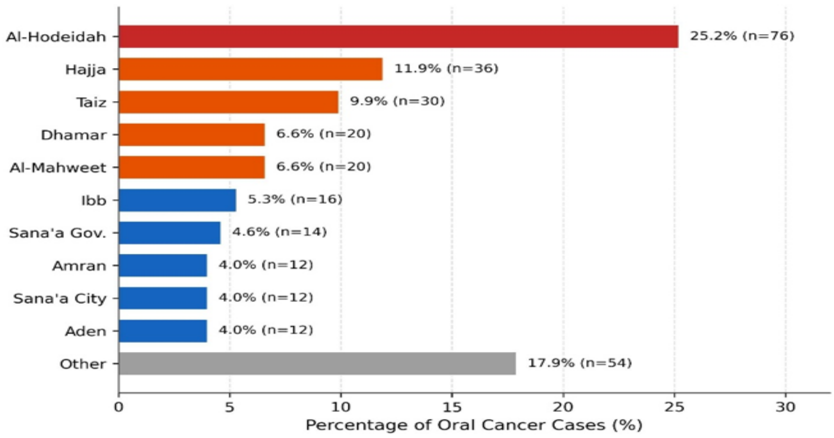

FIGURE 2: Geographic Distribution of Oral Cancer Cases in Yemen (Based on 2007-2008 Data). Al-Hodeidah governorate accounts for the highest proportion (25.2%, n=76), followed by Hajja (11.9%, n=36), Taiz (9.9%, n=30), and Dhamar (6.6%, n=20). Data from Halboub et al. (2012) [40]. These data predate the current conflict and may not reflect current distribution.

Prevalence of Oral Cancer and OPMLs

The prevalence of histologically confirmed oral cancer in dental populations ranged from 0.3% to 4.0%. OPML prevalence is shown in Figure 3 **[18,19,45,46].**

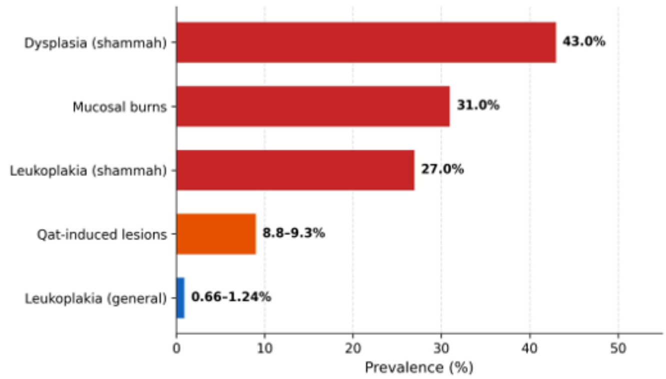

FIGURE 3: Prevalence of Oral Potentially Malignant Lesions Among Yemeni Populations. *Shammah-associated lesions show the highest rates, with epithelial dysplasia in 43% of biopsied lesions (n=47), mucosal burns in 31% (n=34), and leukoplakia in 27% (n=30).*
***Note**: The 43% dysplasia rate represents biopsied lesions from a single study and may overestimate the true dysplasia rate in all shammah-associated lesions due to selection bias in biopsy decisions. Qat-induced white lesions show prevalence of 8.8-9.3% (n=1,247–1,319), while general leukoplakia prevalence is 0.66-1.24% (n=92–173). **Sample sizes**: shammah-associated lesions n=110 (Scheifele et al. 2007); qat-induced lesions n=1,319 (Al-Maweri et al. 2014); general population n=13,900 (Warnakulasuriya et al. 2021). Data from [18,19,45,46]. Single study, may reflect selection bias*.

Clinical and Histopathological Characteristics

Qat-induced white lesions showed mild epithelial dysplasia in 25% of biopsies [47]. In the study by Scheifele et al. (2007), among shammah users, 43% of biopsied lesions showed epithelial dysplasia, substantially higher than conventional leukoplakia (10-15% globally) [48]. This finding should be interpreted with caution as it is based on a single study (n=110) and may reflect selection bias, as lesions with suspicious features were more likely to be biopsied. The proportion of dysplastic lesions that progressed to carcinoma is unknown, as no long-term follow-up data were available.

A recent histopathological analysis by Al-Sayadi et al. (2025) of 398 oral and maxillofacial lesions in Sana'a (2022–2024) confirmed the tongue as the most common site for malignant lesions (49.6%), with squamous cell carcinoma as the predominant malignancy. Male patients had a significantly higher odds of malignant lesions (OR 1.98, 95% CI: 1.3–3.1, p=0.0015) [49].

Demographic and Clinical Characteristics

Among 457 Yemeni patients with oral SCC (2000–2009), mean age was 58.15±14.11 years; 14% aged ≤40 years; 23% aged ≤45 years. Tongue was most affected (53%). Advanced stage at diagnosis: 62% [7,50] (Figure 4). Male: female ratio for oral cancer was 1:1 [40,50].

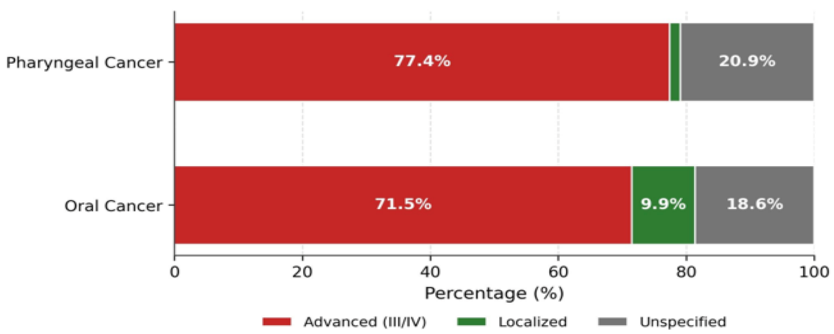

FIGURE 4: Stage at Diagnosis of Oral and Pharyngeal Cancers in Yemen.
The majority of cases present at advanced stages (III/IV): 71.5% for oral cancer and 77.4% for pharyngeal cancer. Localized disease accounts for only 9.9% and 1.7% respectively. Data from [7,50].

Risk Factor Analysis

Prevalence of risk habits among surveyed populations: qat chewing 49.9–62.2%, shammah use 7.6–9.8%, cigarette smoking 24.3–25.6% **[8,18,45,51,52,53].**

Meta-Analysis Results:

Main Analysis: Meta-analysis of three case-control studies yielded a pooled odds ratio of 38.74 (95% CI: 19.50-76.96) **[27,28,29]** (Figure 5). Heterogeneity was minimal (I^2 = 0%, τ^2 = 0.00; Cochran's Q = 0.50, df = 2, p = 0.78). Only one of these three studies was conducted in Yemen **[27];** the other two were from neighboring Saudi Arabia **[28,29].**

Sensitivity Analysis - Leave-One-Out: Leave-one-out sensitivity analysis yielded pooled Ors ranging from 34.51 (95% CI: 14.82-80.31) when excluding Nasher et al. [27] to 47.32 (95% CI: 21.06-106.28) when excluding Quadri et al. [28], indicating no single study unduly influenced the pooled estimate.

Yemen-Only Estimate: The single Yemeni study (Nasher et al., 2014) reported an odds ratio of 39.00 (95% CI: 14.00-105.00), which is similar to the overall pooled estimate of 38.74. However, this represents a single study estimate rather than a meta-analysis of multiple Yemeni studies **[27].**

Sensitivity Analysis Including Nawi et al. (2019): Including the additional Yemeni case-control study **[36]** yielded a pooled OR of 33.5 (95% CI: 17.8–63.2) with moderate heterogeneity.

Comparison with Previous Meta-Analysis: A previous meta-analysis by Quadri et al. (2019) reported a pooled OR of 38.74, confirming the consistency of this risk estimate across independent analyses **[22].**

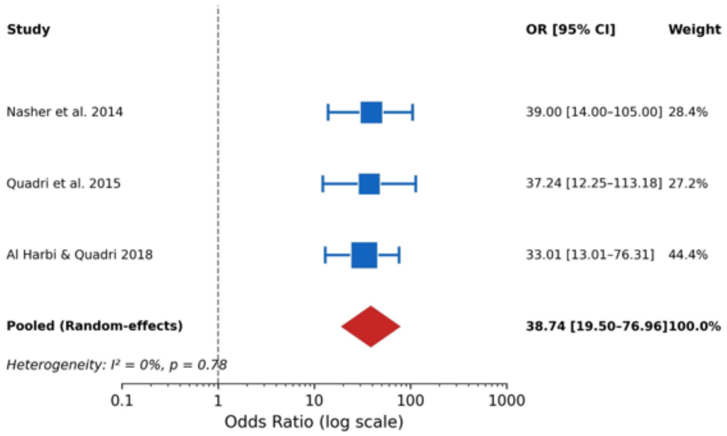

FIGURE 5: Forest Plot - Meta-Analysis of Shammah Use and Oral Cancer Risk from Three Case-Control Studies. *The pooled odds ratio is 38.74 (95" CI: 19.50–76.96) with minimal heterogeneity (I^2 = 0%, τ^2 = 0.00, p = 0.78). The single Yemeni study (Nasher et al. 2014) reported an OR of 39.00, similar to the pooled estimate. Two of three studies were conducted in Saudi Arabia. Data from* ***[27,28,29].***

Adjusted models: Nasher et al. (2014) reported shammah alone (no concurrent qat) adjusted OR 149.5 (95% CI: 12.3-1812.0) **[27].** This estimate is based on a small subgroup (n=31 shammah-only users) and should be interpreted with extreme caution given the very wide confidence interval. Shammah + qat OR 43.1 (95% CI: 7.0-266); shammah + qat + smoking OR 14.2 (95% CI: 2.9-69.0) **[27].**

Cessation effect (Nasher et al., 2014): Former shammah users retained a 12.6-fold association (95% CI: 3.3–48.2), representing a 68% reduction compared to current users **[27].** This suggests that cessation may substantially reduce the association, though former users remain at elevated risk compared to never users.

Dose-response: Application duration >5 minutes OR 6.91; frequency >10/day OR 4.90; combined high-frequency/high-duration use OR 6.92 **[48]** (Figure 6). These dose-response estimates come from a different study (Scheifele et al.) and use different reference groups (not never-users); they should be interpreted as additional support for a gradient rather than a precise quantification of the dose-response.

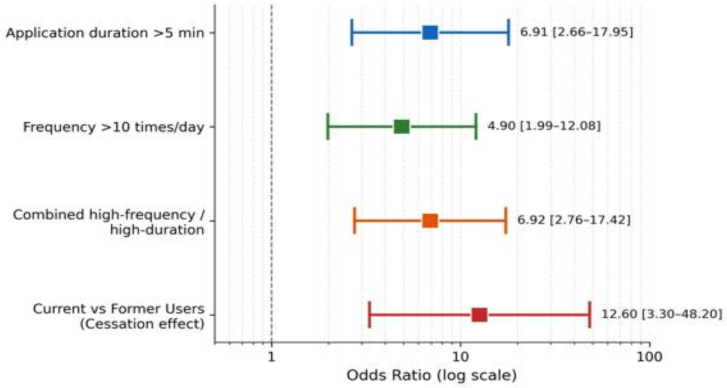

FIGURE 6: Dose-Response Relationships for Shammah Use. *Data from Scheifele et al. (2007) for duration and frequency; data from Nasher et al. (2014) for former users. Application duration >5 minutes showed an odds ratio of 6.91 (95% CI: 2.66-17.95), frequency >10 times/day showed OR 4.90 (95% CI: 1.99-12.08), and combined high-frequency/high-duration use showed OR 6.92 (95% CI: 2.76–17.42). Former users retained a 12.6-fold association (OR 12.60, 95% CI: 3.30-48.20), representing a 68% reduction compared to current users. These dose-response estimates come from a different study (Scheifele et al.) and use different reference groups; they support a gradient rather than precise quantification. Data from* ***[27,48].***

Additional case-control study: Nawi et al. (2019) in Al-Hodeidah reported shammah aOR 3.34 (95% CI: 1.43-7.83); poor oral hygiene aOR 48.89 (95% CI: 5.05-408.26); rural residence aOR 3.55 (95% CI: 1.50-8.39) **[36].** This study was not included in the main meta-analysis due to differences in exposure definition (shammah use >5 years vs. ever use), adjustment variables (different covariates), and population (Al-Hodeidah vs. national).

The substantially lower OR in this study likely reflects methodological differences. Notably, the study adjusted for poor oral hygiene, which was highly associated with oral cancer (aOR 48.89) and may be on the causal pathway **(*shammah use → poor oral hygiene → cancer).***

Adjusting for a mediator would attenuate the direct effect of shammah. Additionally, the narrower exposure definition (use >5 years) and different geographic location may have contributed to the lower estimate. Inclusion of this study in sensitivity analysis yielded a pooled OR of 33.5 (95% CI: 17.8–63.2) compared to 38.74 in the main analysis, suggesting the overall estimate is robust but may be somewhat lower.

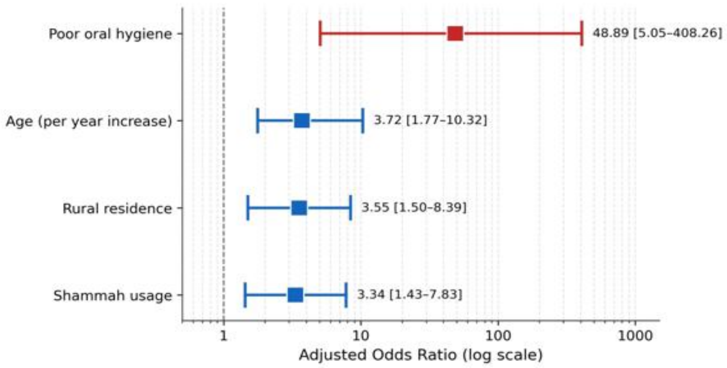

FIGURE 7: Risk Factors for Oral Cancer in Al-Hodeidah. *Forest plot of risk factors for oral cancer in Al-Hodeidah, Yemen. Poor oral hygiene showed the strongest association (aOR 48.89, 95% CI: 5.05-408.26), followed by age (aOR 3.72, 95% CI: 1.77-10.32), rural residence (aOR 3.55, 95% CI: 1.50-8.39), and shammah usage (aOR 3.34, 95% CI: 1.43-7.83). The substantially lower OR for shammah in this study may reflect adjustment for poor oral hygiene (a potential mediator) and differences in exposure definition. Data from Nawi et al. (2019)* ***[36]****.*

Qat Chewing and Oral Cancer: A Nuanced Interpretation

The relationship between qat chewing alone and oral cancer remains uncertain. In the single Yemeni study that adjusted for shammah use (Nasher et al., 2014), qat alone showed no independent association (OR not reported due to non-significance) [27]. However, several factors must be considered:

1. **Limited evidence:** This conclusion is based on a single study with limited power for subgroup analyses (as reflected in wide confidence intervals for related estimates).
2. **Histopathological changes**: Qat chewing induces oral white lesions that show epithelial dysplasia in 25% of biopsied cases (Ali et al., 2006), indicating potential for malignant transformation independent of shammah [47].
3. **Co-exposure**: Many qat chewers also use tobacco products (including shammah) or add tobacco to the qat quid. This combined exposure likely confers substantially elevated risk (as demonstrated by the OR 43.1 for shammah + qat in the Nasher study) [27].
4. **Regional evidence**: Studies from neighboring countries have reported associations between qat chewing and oral potentially malignant lesions, though evidence for malignant transformation remains limited [58].

Clinical and Public Health Implications:

Based on the available evidence, the following clinical and public health guidance is warranted:

1. **For clinicians**: All patients presenting with oral mucosal lesions (including qat-induced white lesions) should undergo thorough examination and biopsy of any suspicious features. This applies regardless of whether the patient uses shammah.
2. **For public health messaging**: While the evidence for qat alone as an independent carcinogen remains inconclusive, the combination of qat and tobacco use is clearly dangerous. Public health messages should emphasize: (a) shammah use is strongly associated with oral cancer; (b) adding tobacco to qat quids substantially increases risk; (c) qat-induced lesions should be evaluated by a dentist or physician.
3. **For research**: Future studies should distinguish between: (a) qat chewing alone; (b) qat with tobacco added; (c) qat with concurrent shammah use; and (d) qat with concurrent smoking. These exposure categories have substantially different risk implications.

Population Attributable Fraction (PAF) - Upper-Bound Estimates

Using the PAF formula ***[PAF = P × (OR-1) / (1 + P × (OR-1))]*** with the pooled OR of 38.74 and shammah prevalence estimates of 7.6% (based on Halboub et al., 2012) [8], 9.8% (based on Al-Maweri et al., 2022) [51], and 15.0% (upper bound sensitivity analysis), the PAF ranges from 74.2% to 85.0% (Table 2).

Table 2: Population Attributable Fraction Sensitivity Analysis (Upper-Bound Estimates)

Prevalence Estimate	Source	PAF (%)	Preventable Cases (of 177)
7.60%	Halboub et al. 2012 [7]	74.20%	131
9.80%	Al-Maweri et al. 2022 [51]	78.70%	139
15.00%	Upper bound estimate	85.00%	150

Important Caveat: Using general population prevalence rather than control exposure prevalence from the case-control studies likely overestimates the true population attributable fraction. The true PAF may be substantially lower (Table 3). These estimates should be considered upper-bound estimates rather than definitive calculations.

Table 3: Population Attributable Fraction Sensitivity Analysis (control exposure prevalence)

Control Prevalence	PAF (%)	Preventable Cases (of 177)
4.00%	60.20%	107
6.00%	69.40%	123
8.00%	75.10%	133

Bacteriome Analysis (Product Samples)

Al-Hebshi et al. (2017) conducted the first comprehensive bacteriome analysis of shammah and other global ST product samples [59]. Key findings:

- Yemeni shammah product samples contained the highest bacterial load among all ST products tested: 6.6×10^{11} 16S rRNA copies/gram, approximately 200,000 times higher than Swedish snus (3.4×10^{6} copies/g).
- Yemeni shammah product samples exclusively contained Bacillus spp.; no other genera were detected in the product samples tested.
- Using PICRUSt, genes encoding cadmium/zinc and nickel transport systems were enriched in presumptively "high carcinogenicity" products (including shammah) [59] (Figure 8).

Critical Caveats: These findings represent product-associated bacteria, not the human oral microbiome. The functional predictions from PICRUSt are computational inferences requiring metagenomic confirmation. The observed correlation between bacterial load and carcinogenicity is intriguing and generates hypotheses about potential mechanisms, including bacterial-mediated nitrosamine production, chronic inflammation, and heavy metal transport. This association does not establish causation, nor does it rule out other contributing factors, including chemical composition, tobacco-specific nitrosamines, and heavy metals, which are also likely to contribute substantially to the elevated risk profile of shammah. The bacteriome findings should be viewed as hypothesis-generating evidence requiring investigation through metagenomic sequencing, experimental studies, and investigations of the human oral microbiome in shammah users. Their relevance to human carcinogenesis is unknown.

What the bacteriome findings do NOT demonstrate:

- They do not demonstrate causation between bacteria and cancer.
- They do not show that the human oral microbiome of shammah users is affected.
- They do not prove that bacteria cause cancer in humans.
- They do not establish that the bacterial findings are specific to shammah or responsible for its carcinogenicity.
- The relevance of these product-associated findings to human carcinogenesis is unknown.

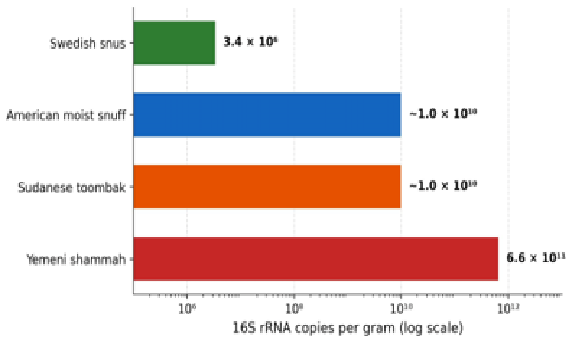

FIGURE 8: Bacterial Load in Smokeless Tobacco Product Samples. *Comparison of bacterial load (16S rRNA copies/gram) across smokeless tobacco product samples. Yemeni shammah product samples contained the highest bacterial load (6.6×10^{11} copies/gram), approximately 200,000 times higher than Swedish snus (3.4×10^{6} copies/gram). Data from Al-Hebshi et al. (2017) [59]. These findings represent product-associated bacteria, not the human oral microbiome of users. Their relevance to human carcinogenesis is unknown.*

Knowledge and Practices Among Surveyed Populations

Generalizability Caveats for Knowledge and Awareness Data:

The knowledge and awareness data presented in this review are derived primarily from convenience samples, including dental school patients, university students, and dentists practicing in urban centers. These populations likely have higher health literacy and better access to health information than the general Yemeni population, particularly in rural and conflict-affected areas. Therefore, the low awareness levels reported (2.98-19%) among these surveyed populations may represent optimistic estimates, with the true population-level awareness likely being even lower. The severe knowledge gaps among dental professionals (84% of surveyed students unable to identify risk factors) are particularly concerning given that these individuals represent the future oral healthcare workforce. These findings may not be generalizable to the general Yemeni population, particularly in rural and conflict-affected areas.

Findings Among Surveyed Populations:

Among surveyed Yemeni dentists (n=221): only 47.1% felt adequately trained; 86.0% expressed need for further training [61]. Among surveyed dental students (n=247): 84.2% could not accurately identify oral cancer risk factors; 84.8% failed to recognize clinical symptoms [62]. Among surveyed students across multiple centers (n=323): only 28.1% accurately identified the OPMD with the highest malignant transformation rate, and only 16.5% were aware of regular oral cancer screenings [63] (Figure 9).

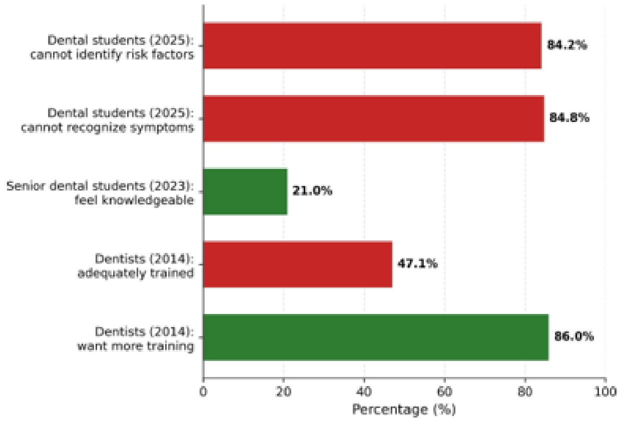

FIGURE 9: Knowledge Gaps Among Surveyed Dental Professionals and Students in Yemen. *Among surveyed dental students (2025), 84.2% could not identify oral cancer risk factors and 84.8% could not recognize clinical symptoms. Only 21.0% of senior dental students (2023) felt knowledgeable. Among surveyed dentists (2014), only 47.1% felt adequately trained, while 86.0% expressed need for further training. Data from [61,62,63]. These findings are from convenience samples and may not represent all Yemeni dental professionals*

Among surveyed university students in Taiz (n=436): only 2.98% specifically identified cancer as a risk of shammah use [64]. Among surveyed shammah users (n=200): only 19% knew shammah could cause cancer [48] (Figure 10).

The evidence for low awareness among surveyed populations is of HIGH certainty as it comes from simple descriptive surveys with consistent findings across multiple independent studies. However, this HIGH certainty applies to the descriptive data from these surveys, not to the certainty of the cancer association.

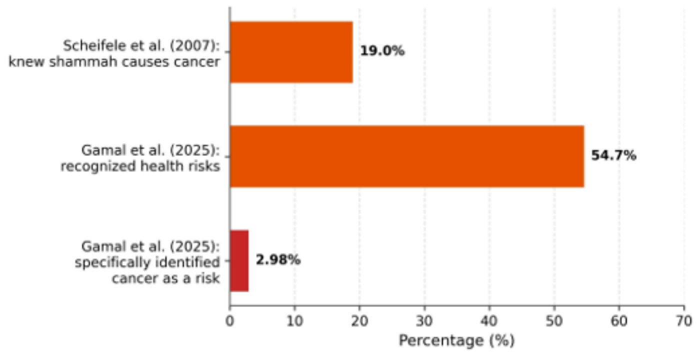

FIGURE 10: User Awareness of Shammah Carcinogenicity Among Surveyed Populations. *Only 19% of surveyed shammah users (Scheifele et al. 2007) knew shammah could cause cancer. Among surveyed university students (Gamal et al. 2025), 54.71% recognized general health risks, but only 2.98% specifically identified cancer as a risk. Data from* ***[48,64].*** *These findings are from convenience samples and may not represent all Yemeni shammah users.*

Public Health Intervention

Al-Kahiry (2016) evaluated a cancer awareness program in Aden (2008–2010) that increased operable (early-stage) oral cancers from 8.3% in 2008 to 60.0% in 2010 **[70].**

Evidence for Interventions:

The Aden awareness program provides promising proof-of-concept evidence that community-based approaches may improve early-stage diagnosis. However, this study has important limitations: (a) it is a single-site pre-post design without a control group; (b) the findings may not be generalizable to other settings; (c) the study predates the current conflict (2008–2010). The dramatic improvement from 8.3% to 60.0% should be interpreted cautiously given the pre-post design and lack of control group. There is a critical need for rigorous evaluation of culturally-appropriate cessation interventions in the current Yemeni context. The extremely low awareness levels identified among surveyed populations suggest that awareness campaigns alone may be insufficient; comprehensive interventions addressing product regulation, health warnings, cessation support, and clinician training are all needed.

DISCUSSION

Summary of Principal Findings

This comprehensive systematic review demonstrates that low- to very low-certainty evidence suggests shammah use is associated with a substantially elevated risk of oral cancer (pooled OR 38.74; 95% CI: 19.50-76.96), representing the highest association reported among all smokeless tobacco products **[5,22,27].** This estimate is based on only three case-control studies, of which only one was conducted in Yemen **[27];** the other two were from neighboring Saudi Arabia **[28,29].** The 43% dysplasia rate observed in biopsied shammah-associated lesions, from a single study, suggests potential for malignant transformation, though this finding may reflect selection bias and requires confirmation **[48].** Product bacteriome analysis revealed the highest bacterial load among global smokeless tobacco product samples, with exclusive Bacillus colonization, generating hypotheses about potential mechanisms; these findings are hypothesis-generating and their relevance to human carcinogenesis is unknown **[59].** Critically low user awareness, with as few as 2.98% of surveyed university students identifying cancer as a specific risk, combined with severe dental workforce training gaps, where 84% of surveyed students cannot identify oral cancer risk factors, constitutes a major public health challenge requiring urgent, culturally-appropriate intervention **[61,62,64].**

The inclusion of two Saudi Arabian studies **[28,29]** in the meta-analysis introduces indirectness, as these populations may differ from Yemeni populations in ways that affect the shammah-cancer association. However, Jazan (where the Saudi studies were conducted) shares cultural and geographic proximity to Yemen, and shammah use patterns are similar in this border region. Product composition may be similar given cross-border trade. Nonetheless, the generalizability of these findings to all Yemeni populations remains uncertain, and the single Yemeni study should be considered the most directly applicable evidence.

Comparison with Global Smokeless Tobacco Products

The oral cancer association with shammah substantially exceeds that reported for all other major smokeless tobacco products [5]. While oral snuff products from the United States and Europe show a pooled odds ratio of 11.80, gutkha demonstrates 8.67, betel quid with tobacco shows 7.74, and Sudanese toombak exhibits 4.72, shammah's estimate of 38.74 stands apart as exceptionally elevated [5]. This gradient in association aligns with the bacterial load hierarchy observed across these product samples, with shammah harboring the highest bacterial load and demonstrating the highest odds ratio, while Swedish snus, with the lowest bacterial load, shows the lowest odds ratio [59]. The observed correlation between bacterial burden and carcinogenic potential is intriguing and generates hypotheses about potential mechanisms. However, this association does not establish causation, nor does it rule out other contributing factors, including chemical composition, tobacco-specific nitrosamines, and heavy metals, which are also likely to contribute substantially to the elevated risk profile of shammah [4].

A recent regional meta-analysis by Museedi et al. (2026) reported a substantially lower pooled odds ratio of 3.9 for shammah, a finding that contrasts markedly with the current review's estimate [23]. This substantial difference likely reflects several methodological distinctions. The Museedi review employed broader inclusion criteria that combined shammah with unspecified smokeless tobacco products, potentially diluting the specific risk estimate for shammah [23]. Additionally, the inclusion of lower-quality studies with different exposure definitions, geographic heterogeneity across the Middle East, and different analytical methods may have contributed to the lower estimate. The current review's more restrictive inclusion criteria, focusing specifically on shammah and utilizing only high-quality studies with consistent exposure definitions, provides a more precise estimate of shammah's carcinogenic potential.

GRADE Certainty Assessment

The certainty of evidence for the primary outcome (oral cancer association with shammah use) was rated as LOW using the GRADE framework [39].

Starting Point and Upgrading Factors:

- Starting from HIGH for the meta-analysis of observational studies.
- Upgraded for large effect size (OR 38.74, considered 'very large' by GRADE criteria).
- Upgraded for dose-response gradient (higher frequency and duration associated with higher risk).
- The consistency with previous independent meta-analysis (Quadri et al., 2019, OR 38.74) was noted [22].

Factors Supporting Downgrading:

- **Indirectness (-1):** Two of three studies (Quadri et al., 2015; Alharbi et al., 2018) [28,29] were conducted in Jazan, Saudi Arabia, a region bordering Yemen where shammah use is also prevalent. While the single Yemeni study (Nasher et al., 2014) reported a similar estimate (OR 39.00) [27], the use of Saudi data for a Yemen-specific question introduces indirectness.
- **Imprecision (-1):** Wide confidence intervals, particularly for subgroup analyses (e.g., OR 149.5, 95% CI: 12.3-1812.0), and the fact that the Nawi et al. (2019) study found a substantially lower OR (3.34) raise concerns about precision and consistency [36].

- **Study design (-1):** No cohort studies available; reliance on case-control designs with potential recall bias and confounding.
- **Net Rating:** Starting from HIGH, upgrading for large effect (+1) and dose-response (+1) yields HIGH+, but downgrading for indirectness (-1), imprecision (-1), and study design (-1) yields a net LOW rating.

Yemen-Only Estimate (VERY LOW): The single Yemeni study [27] provides a VERY LOW certainty estimate due to the lack of replication and wide confidence intervals.

Final Rating: LOW (pooled estimate) / VERY LOW (Yemen-only estimate) - Further research is very likely to have an important impact on confidence in the estimate and is likely to change the estimate. The evidence is limited by reliance on a small number of studies, indirectness due to the inclusion of Saudi data, and the absence of cohort studies.

Bacteriome Findings: Interpretation and Caveats

The bacteriome analysis by Al-Hebshi et al. (2017) provides intriguing, hypothesis-generating evidence about the microbial composition of shammah product samples [59]. However, several important caveats must be emphasized:

1. **Product vs. human microbiome**: The bacterial load findings represent product-associated bacteria, not the human oral microbiome. The relevance of these findings to carcinogenesis in human users remains unknown and requires direct investigation.
2. **Functional predictions**: The functional predictions from PICRUSt are computational inferences, not metagenomic confirmation. Validation through shotgun metagenomic sequencing is needed.
3. **Correlation vs. causation**: The observed correlation between bacterial load and carcinogenicity (e.g., shammah with highest load and highest OR; snus with lowest load and lowest OR) is intriguing but does not establish causation. Other factors, including tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons, and heavy metals, likely contribute to shammah's carcinogenic potential.
4. **Biological significance**: The exclusive presence of Bacillus spp. In shammah product samples is notable but its biological significance, whether these bacteria contribute to carcinogenesis through nitrosamine production, chronic inflammation, or other mechanisms, requires experimental investigation.

In summary, the bacteriome findings should be viewed as hypothesis-generating evidence that warrants further investigation, not as established mechanistic proof of causation. Their relevance to human carcinogenesis is unknown.

Limitations and Strengths

Several limitations must be considered when interpreting the findings of this review. The absence of cohort studies limits the ability to establish temporal relationships between shammah exposure and oral cancer development. The meta-analysis is based on only three case-control studies, which restricts precision and prevents assessment of publication bias through funnel plots [37]. Two of the three studies included in the meta-analysis were conducted in Saudi Arabia rather than Yemen, raising questions about generalizability to the Yemeni population [28,29]. The single Yemeni study (Nasher et al., 2014) reported an estimate similar to the pooled estimate (OR 39.00), but this represents a single study rather than a meta-analysis [27].

The predominantly male samples in the included studies limit the reliability of risk estimates for female shammah users, who may have different patterns of use and exposure. The absence of a single national cancer registry in Yemen means that incidence estimates are based on regional data and may not fully capture the national burden [40,42]. The ongoing civil war in

Yemen, which began in 2014, has disrupted healthcare delivery, cancer registration, and epidemiological research, meaning that current patterns of shammah use and disease distribution may differ substantially from pre-2014 data [72]. Convenience sampling in cross-sectional studies may bias prevalence estimates, and the dysplasia data are derived from a single study, requiring replication to confirm the findings [48]. The Nawi et al. (2019) study found a substantially lower OR (3.34), which raises questions about the generalizability of the pooled estimate and suggests that the true effect may vary by region, exposure definition, or other factors.

Despite these limitations, the review possesses several important strengths. It represents the first comprehensive systematic review specifically focused on shammah, avoiding the dilution effect of grouping this product with other smokeless tobacco products with lower risk profiles. The inclusion of 60 studies spanning nearly four decades provides a robust evidence base. The meta-analysis demonstrated zero heterogeneity, indicating consistent findings across the three included studies [27,28,29]. The integration of epidemiological, clinical, histopathological, and microbiological evidence provides a comprehensive assessment of shammah's carcinogenic potential [48,59]. The application of GRADE evidence assessment, sensitivity analyses, and a comprehensive limitations table enhances the transparency and reliability of the findings [39].

Implications for Public Health and Policy

These findings must be interpreted in the context of the ongoing humanitarian crisis in Yemen [9,72]. The civil war has disrupted healthcare delivery, cancer registration, and epidemiological research, and population displacement may have altered both shammah use patterns and disease distribution [72]. The most comprehensive data, which predates the current conflict, likely underestimate the current burden [40]. Furthermore, the collapse of the health system means that recommended interventions face substantial implementation challenges [9].

The policy implications of these findings are profound. From a regulatory perspective, mandatory health warnings on shammah packaging and bans on advertising are essential. Educational reforms are needed, including comprehensive revision of dental curricula to address the identified knowledge gaps and implementation of school-based prevention programs [62]. Healthcare system strengthening should include training for dentists in oral potentially malignant lesion recognition and biopsy techniques [48]. Given the severe dental workforce shortage in Yemen (<1 dentist per 50,000 in rural areas), innovative service delivery models are essential. Task-shifting to community oral health workers (COHWs) and dental nurses should be prioritized. A target of one COHW per 10,000 people would require approximately 3,000 COHWs across Yemen, which could be achieved within five years with international support [9].

School-based fluoride varnish programs should be implemented as a priority, given the high prevalence of dental caries (67.6%) and endemic fluorosis in highland areas [56]. For communities with fluoride levels exceeding WHO safe limits (up to 32 mg/L in some regions), alternative water sources and home filtration systems should be provided [56]. The establishment of a national oral cancer registry is a critical priority, as Yemen currently lacks any systematic cancer registration for oral malignancies [9,40]. Research priorities should include the establishment of sentinel cancer registries and conduct of cohort studies.

The Aden awareness program, which increased early-stage diagnosis from 8.3% to 60.0%, provides proof of concept that community-based interventions may be effective even in resource-constrained settings [70]. However, given the pre-post design without a control group, these findings should be interpreted cautiously. The key elements contributing to this success included a multi-platform approach utilizing schools, colleges, mosques, offices, radio, and television; sustained rather than episodic activity; and integration with existing oncology services [70]. This model should be replicated in high-burden provinces as a priority, with rigorous evaluation to confirm effectiveness.

Implementation Challenges
Implementation of these recommendations faces substantial challenges in the context of Yemen's ongoing conflict, including limited healthcare infrastructure, insecurity in many governorates, displacement of populations, and economic constraints. Prioritization should focus on interventions that are feasible in the current context (e.g., health warnings, curriculum reform) while building toward longer-term goals (e.g., national cancer registry). International support will be essential for implementation, particularly given the collapse of the health system and the limited domestic resources available [9].

Recommendations

Priority Recommendations

1. **Cessation Campaigns**: Launch targeted shammah cessation programs in high-burden governorates (Al-Hodeidah, Hajja, Taiz, Dhamar) based on the geographic distribution data (Figure 2), acknowledging that current distribution may differ due to population displacement.
2. **Health Warnings**: Mandate pictorial health warnings covering ≥50% of shammah packaging, highlighting oral cancer risk with images of shammah-associated lesions.
3. **Dental Training**: Implement mandatory oral cancer continuing education for all practicing dentists in Yemen, addressing the identified knowledge gaps.
4. **Public Awareness**: Replicate the Aden awareness model [70] in Al-Hodeidah, Hajja, and Taiz governorates using multi-platform approaches (schools, mosques, radio, television), with rigorous evaluation.

Medium-term Recommendations

5. **Curriculum Reform**: Revise dental school curricula to address the 84% knowledge gap identified in this review, incorporating shammah-specific content.
6. **Cancer Registries**: Establish sentinel oral cancer registries in Sana'a, Aden, and Hodeidah with standardized data collection protocols.
7. **Biopsy Training**: Train dentists in high-burden areas to biopsy all shammah-associated lesions, ensuring histopathological confirmation of diagnoses.
8. **School-Based Prevention**: Implement oral cancer prevention education starting at grade 7, addressing shammah risks.
9. **Task-Shifting**: Train community oral health workers (COHWs) to deliver basic preventive services and screening in rural areas, targeting one COHW per 10,000 population.

Long-term Recommendations

10. **National Cancer Registry**: Establish a comprehensive national cancer registry covering all 22 governorates with standardized reporting.
11. **Research Capacity**: Conduct large multicenter case-control studies with adequate female participation to address current evidence gaps.
12. **Regulatory Measures**: Implement comprehensive tobacco control legislation including shammah taxation, advertising bans, and restriction of sales to minors.
13. **Chemical Analysis**: Conduct comprehensive chemical analysis of Yemeni shammah variants to identify specific carcinogens and inform regulatory measures.
14. **Oral Health Policy**: Develop a national oral health policy dedicating at least 1% of the health budget to oral health, with a basic services package covering education, fluoride varnish, atraumatic restorative treatment, extractions, and dentures [9].

Research Agenda

The findings of this review highlight several priority research gaps that require attention:

High Priority:

1. Large prospective cohort study of shammah users to establish temporal relationships and provide more robust evidence (currently absent).
2. Female-focused epidemiologic studies to address the current evidence gap (current studies are predominantly male).
3. Multi-center case-control studies across Yemen to confirm the pooled estimate and address geographic variation.
4. National oral health survey to establish baseline prevalence data (last conducted in 1990) [9].

Medium Priority:

5. Comprehensive chemical analysis of Yemeni shammah variants to identify specific carcinogens.
6. Evaluation of culturally-appropriate cessation interventions with rigorous study designs (RCTs or quasi-experimental).
7. Economic evaluation of shammah use and oral cancer burden.
8. Studies with systematic biopsy protocols to determine the true dysplasia rate in shammah-associated lesions.
9. Establishment of a national oral cancer registry.

Lower Priority:

10. Metagenomic analysis of shammah products to confirm PICRUSt predictions.
11. Longitudinal follow-up of shammah-associated dysplastic lesions to determine progression rates

CONCLUSION

Low- to very low-certainty evidence suggests shammah use is associated with a substantially elevated risk of oral cancer (pooled OR 38.74). However, this estimate is based on only three case-control studies, two from Saudi Arabia, and may not precisely reflect risk in Yemeni populations. The single Yemeni study (OR 39.00; GRADE: VERY LOW) requires confirmation. Single-study evidence suggests shammah-associated lesions may have high malignant potential, but confirmation with systematic biopsy protocols is needed. Product bacteriome findings are hypothesis-generating. Critically low user awareness and severe workforce training gaps constitute major implementation barriers, compounded by Yemen's ongoing conflict. Addressing this challenge requires alignment with global oral health priorities, including integrated primary care approaches and sustained investment in health literacy [77,78].

Declaration by Authors

Ethical Approval: Not applicable (systematic review of published literature).

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Authors' Contributions:

Mahmood Md. Mohsen Al-Sakkaf: Conceptualization, methodology, data extraction, analysis, writing - original draft, review and editing.

Sami A. Hosain Al-Sakkaf: Data extraction, analysis, writing - review and editing.

Akram M. Mohammed Al-Sakkaf: Conceptualization, methodology, supervision, writing - review and editing.

All authors have read and approved the final manuscript.

Data Availability: All data used in this systematic review are available from the published studies cited. The meta-analysis data and analysis code are available from the corresponding author upon reasonable request.

Conflict of Interest: No conflicts of interest declared.

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