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Cancer and Potentially Malignant Disorders

Cultural Practices and Oral Cancer Risk in South America: An Evidence- and Experience-Based Position Paper

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ABSTRACT

Background: Oral cavity squamous cell carcinoma (OSCC) remains a major public health challenge worldwide. In South America, its epidemiology is influenced by culturally embedded practices that remain underrepresented in the international literature.

Aims: To critically examine region-specific exposures that may contribute to oral carcinogenesis and to identify major knowledge gaps relevant to OSCC prevention and early detection in South America.

Materials and Methods: This evidence-informed position paper was developed through consensus among specialists from South American referral centers and a structured appraisal of the available literature, focusing on chimó use, coca leaf chewing, reverse smoking, hot mate consumption, and charcoal-grilled meat intake.

Results: Current evidence suggests that these practices involve biologically plausible mechanisms, including thermal injury, chronic mechanical irritation, exposure to potentially carcinogenic chemical compounds, and persistent mucosal inflammation, that may promote carcinogenesis.

Discussion: The strength of the available evidence varies considerably across exposures, and several associations remain hypothesis-generating and require further epidemiological, mechanistic, and molecular validation.

Conclusion: This position paper identifies major knowledge gaps and proposes a regional research agenda aimed at improving risk assessment, prevention strategies, and the early detection of OSCC in South America.

1 | Introduction

Oral squamous cell carcinoma (OSCC) accounts for the vast majority of malignancies arising in the oral cavity and remains a major global health challenge. In 2022, oral cavity cancer accounted for approximately 42% of the 758,000 new cases of lip, oral cavity, and pharyngeal cancers worldwide, making it the most common subsite within this group (Rumgay et al. 2026). In South America, oral cavity cancer represents a significant public health challenge, with a markedly uneven distribution across the region (Louredo et al. 2023). This heterogeneity in regional risk profiles underscores the need for subsite-specific epidemiological data to guide prevention strategies, early detection initiatives (e.g., visual oral examination), and resource allocation

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within cancer control policies tailored to regional realities (International Agency for Research on Cancer [IARC] 2023; Martínez-Ramírez et al. 2024).

The global distribution of oral cancer is markedly heterogeneous and closely reflects regional patterns of exposure to behavioral, environmental, and culturally embedded carcinogenic or potentially carcinogenic agents (Bouvard et al. 2022). In Western Europe and North America, the traditional risk profile is largely dominated by the synergistic interaction between tobacco use and alcohol consumption. High-risk human papillomavirus (HPV), particularly HPV16, is a major etiological factor in oropharyngeal squamous cell carcinoma; however, its contribution to OSCC appears to be considerably more limited (Johnson et al. 2020; Khan et al. 2025). In contrast, some of the highest incidence rates worldwide are observed in South and Southeast Asia, where the widespread use of betel quid, areca nut, and different forms of smokeless tobacco (ST) constitutes a major etiological driver (Guha et al. 2014; Gupta et al. 2017; IARC 2007, 2012; Warnakulasuriya 2009). The risks associated with these practices are often dose-dependent and shaped by sociocultural factors, including sex differences and socioeconomic context, which may further intensify mucosal exposure to carcinogenic and irritating stimuli and increase the risk of malignant transformation (Museedi et al. 2026). In South Asia, areca nut, consumed either alone or in combination with tobacco, has been classified as a Group 1 carcinogen by the IARC (2004) and Ray and Gupta (2025). Its role in oral carcinogenesis is supported by strong epidemiological evidence from cohort and case–control studies (Guha et al. 2014). This OSCC risk profile is therefore characterized by culturally entrenched carcinogenic exposures with well-established biological underpinnings. Together, these exposures illustrate how region-specific cultural habits contribute to distinct epidemiological patterns of OSCC, reinforcing the need to interpret OSCC risk within its broader sociocultural and behavioral context (Krishna Rao et al. 2013).

Recent regional studies have identified distinctive clinical and epidemiological features among South American populations that differ from those observed elsewhere. Beyond established risk factors such as tobacco use, alcohol consumption, and poor oral hygiene, culturally embedded practices such as hot mate consumption, coca leaf chewing, *chimó* use, and reverse smoking (RS) may contribute to OSCC risk in specific subpopulations (Gilligan et al. 2024). Rooted in local traditions and social identity, these behaviors represent region-specific exposure patterns that are uncommon elsewhere and warrant focused epidemiological, clinicopathological, and molecular investigation to clarify their potential role in OSCC development (Dutra et al. 2026).

In South America, the etiological landscape of oral cancer appears to be more complex and remains comparatively undercharacterized (Franco et al. 1989). Although the synergistic effect of tobacco and alcohol remains a central determinant, some populations in Colombia and Venezuela, as well as those in the Southern Cone (particularly Argentina, Uruguay, Paraguay, and southern Brazil), exhibit epidemiological patterns that may not be fully explained by these traditional risk factors alone. These patterns may be partly attributable to Indigenous traditions and folk practices (Moore et al. 2014). Unlike South and Southeast Asia, where orally consumed masticatory carcinogens dominate the risk profile, the Southern Cone is characterized by exposure practices of a different nature.

The objective of the present position paper was to promote a regionally grounded, evidence-based examination of culturally embedded risk factors for OSCC in South America, as identified in emerging research. Drawing on published epidemiological evidence and the accumulated clinical experience of specialized diagnostic centers across the region, this article critically examines the aforementioned traditional practices within the broader context of established carcinogenic determinants.

2 | Methods

This evidence- and experience-informed position paper was developed through a multicenter collaboration among 10 clinicians and researchers from South American centers, prompted by the limited representation of region-specific oral cancer risk practices in the international literature. Participants contributed clinical and academic perspectives on culturally specific exposures observed in their respective countries. The scope and selected exposures were defined through virtual meetings and an in-person meeting held in Córdoba, Argentina, in September 2025. Exposures were prioritized according to their clinical relevance, epidemiological impact, and existing knowledge gaps. Consensus was reached through iterative discussion, with divergent views resolved collectively. The selection was also informed by a multicenter study of OSCC and oral potentially malignant disorders (OPMDs) in Latin America that identified differences in exposure patterns across populations (Gilligan et al. 2024).

PubMed/MEDLINE, Scopus, the Scientific Electronic Library Online (SciELO), and the Latin America and the Caribbean Literature on Health Sciences (LILACS) databases were searched between October 2025 and May 2026, with supplementary searches conducted in Google Scholar and no publication date restrictions. Search terms related to oral cancer/OPMDs ("oral cancer", "oral squamous cell carcinoma", and "oral potentially malignant disorders") were combined with terms related to the selected exposures ("chimó", "smokeless tobacco", "coca leaf chewing", "reverse smoking", "hot mate", "mate consumption", and "charcoal-grilled meat"). Geographic terms, including "South America" and the names of individual South American countries, were used when appropriate, and the search strategy was adapted to each database. Epidemiological, clinical, experimental, and review articles were considered. Given the heterogeneity of the evidence and the objectives of this article, no formal systematic review methodology or risk-of-bias assessment was undertaken.

3 | *Chimó* as a Form of ST

The use of ST has deep roots in several regions and encompasses well-known products such as Swedish snus, American snuff, South Asian *gutkha*, Sudanese *toombak*, and Venezuelan *chimó* (Dutra et al. 2026; Rumgay et al. 2024). *Chimó* is an alkalized and flavored tobacco extract. The alkaline additive typically consists of sodium bicarbonate or caustic soda derived from ashes, resulting in an extremely potent product (Kamen-Kaye 1975). Globally, ST products are used through diverse routes, including

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FIGURE 1 | Geographical distribution of culturally embedded practices potentially associated with oral cancer risk in South America.

oral, nasal, and topical application. Commonly chewed preparations include betel quid and pan masala (e.g., zarda and gutkha). Snuff products are further classified according to their moisture content. The inherent heterogeneity of these products poses a significant methodological challenge for public health research. Although ST is a major etiological driver of OSCC in South Asia, substantial variation among ST products has been reported (Hecht et al. 2022). These differences in chemical profiles are primarily attributable to variations in manufacturing processes and product-specific chemical composition, particularly the concentration of the carcinogen N′-nitrosonornicotine. Thus, the pathophysiological and health effects of *chimó* cannot be equated with or directly compared with those of North American snuff.

Some authors consider the term "chewing tobacco" inaccurate because *chimó* is not chewed; rather, its use is more appropriately described as sucking or allowing the product to dissolve. The tobacco paste is placed in the vestibular sulcus, adjacent to the gingiva and teeth, where it dissolves slowly, similar to a piece of candy, and increases salivary flow. Users may either suck and swallow or expectorate the resulting saliva. As the product dissolves, its constituents are absorbed through the oral mucosa, eliciting sensations of pleasure, reduced appetite, heightened alertness, and even relief from toothache. These perceived effects may help explain its use among children and adolescents (Bermúdez et al. 2017).

Chimó contains a complex chemical matrix comprising nicotine, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, aldehydes, and heavy metals. Although tobacco leaf is the primary raw material, the final composition varies considerably according to regional manufacturing traditions. Its preparation involves a wide range of additives, including alkaline agents (e.g., wood ash and lye) and flavoring agents ranging from sweeteners (e.g., honey, molasses, and brown sugar) to aromatics (e.g., vanilla, cocoa, nutmeg, and cloves) (Asthana et al. 2019; Bermúdez 2011). Some formulations incorporate unconventional ingredients (e.g., deer antler, banana, and potato peels) and toxic contaminants (e.g., arsenic) have also been detected (Asthana et al. 2019). Because of market competition, producers regard these "seasoning secrets" as proprietary information. From a pharmacological perspective, the high nicotine content confers substantial addictive potential. Although nicotine absorption is slower than with inhaled tobacco, regular users often achieve higher systemic nicotine concentrations than those observed in cigarette smokers (Benowitz et al. 1988).

In Venezuela and the Andean regions of South America (Figure 1), *chimó* consumption represents a complex phenomenon that extends beyond chemical dependence and is deeply embedded in the region's social, cultural, and historical fabric. Although its origins date back to the Spanish or Portuguese colonial era as a strictly artisanal practice, the product has undergone a substantial transition toward industrial-scale manufacturing, further complicating the standardization of toxicological studies (Bermúdez 2011). The association between ST use and OPMDs varies considerably across regions (Pedroso et al. 2023), partly because of differences in the chemical composition and manufacturing processes of regional products. In Brazil, ST is derived from *fumo de rolo* (also known as *fumo de corda* or *fumo crioulo*), a handcrafted tobacco typical of the northeastern region of the country and characterized by its intense flavor, twisted form, and sun-curing process. It is typically finely shredded before use. Notably, the chemical composition of Venezuelan *chimó* precludes its direct equivalence with other ST products available on the market. *Chimó* remains an important putative contributor to OPMD and OSCC in the Venezuelan population. In this context, a meta-analysis of

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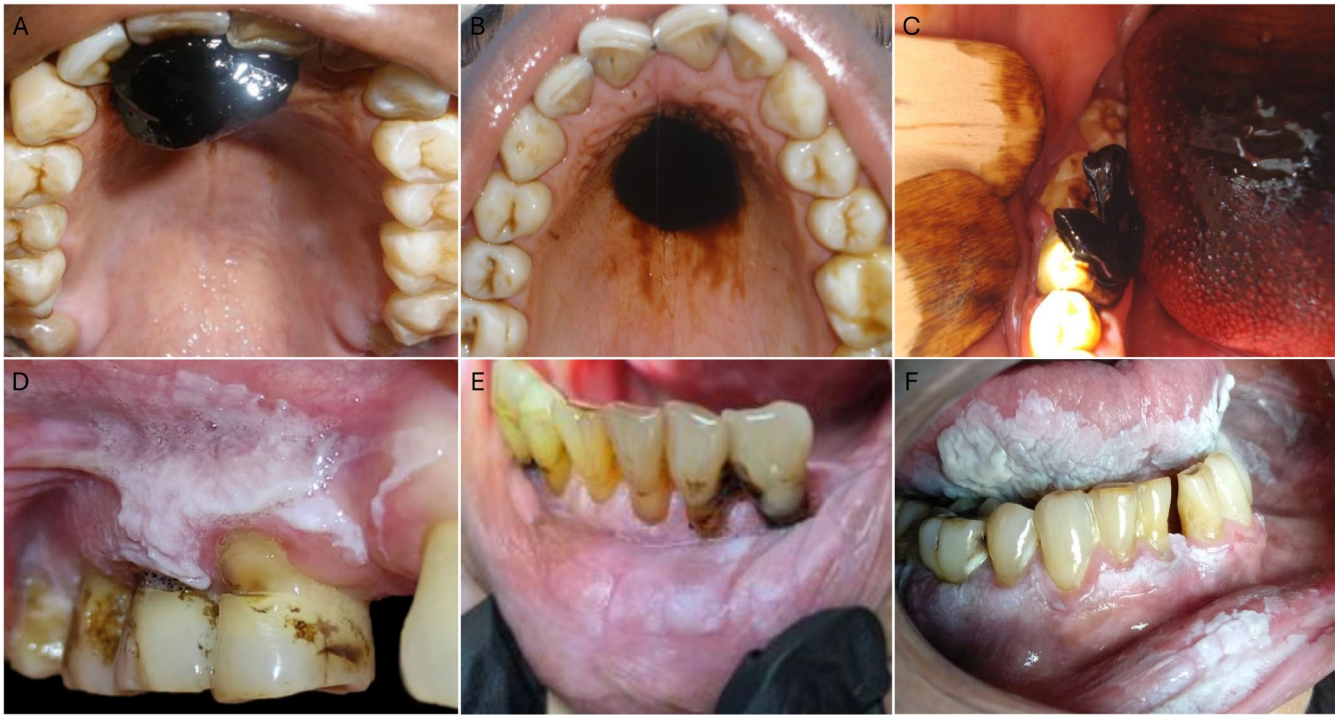

FIGURE 2 | Clinical spectrum of *chimó*-associated oral lesions. (A–C) *Chimó* placed in direct contact with the oral mucosa, including the hard palate and posterior mandibular vestibule, with adjacent dark staining of the dorsal surface of the tongue and teeth. (D) Extensive white patch involving the right maxillary gingiva and adjacent vestibular mucosa, characterized by an irregular shape, rough surface, poorly defined margins, and associated extrinsic brown staining of the teeth. (E) Diffuse, heterogeneous white patch involving the anterior mandibular gingiva and extending to the lower labial mucosa. Note the brown-black extrinsic staining of the anterior mandibular teeth. (F) Extensive multifocal white patches involving the lateral border and ventral surface of the tongue, mandibular attached gingiva, and lower labial mucosa, with irregular contours, a corrugated or verrucous surface, and poorly defined margins.

ST use in the Pan-American region reported a pooled prevalence estimate of 33.4% for Venezuela, the highest among the countries analyzed. However, this estimate was derived from only two studies with small samples and should not be interpreted as nationally representative (Pedroso et al. 2023).

Clinically, the initial manifestations of *chimó* use include white patches of the oral mucosa localized to the site of contact. The adjacent dentition frequently exhibits extrinsic staining and, over time, pronounced occlusal or surface wear. With continued exposure, these white patches may extend to larger areas of the oral mucosa, substantially increasing the risk of malignant transformation. Consequently, OSCC is notably frequent among habitual *chimó* users. Histopathologically, these lesions may exhibit thick layers of surface orthokeratin (hyperorthokeratosis), together with varying degrees of epithelial dysplasia. Associated focal melanosis may also be observed. Based on our clinical experience, we hypothesize that *chimó*-associated lesions may progress from localized white patches to more extensive mucosal involvement with potentially greater malignant potential (Figure 2). The presence of alkalizing agents and heavy metals (e.g., arsenic) in the chemical matrix of *chimó* may exacerbate cellular damage and promote oral carcinogenesis. Therefore, early detection and recognition of the distinct toxicological profile of *chimó* are essential to mitigating the burden of OSCC in the Venezuelan population. Further studies in tobacco-producing regions are needed to determine whether tobacco production is associated with increased use and exposure to OSCC-related risk factors.

4 | Yerba Mate Consumption

In the Southern Cone of South America, habitual consumption of *Ilex paraguariensis* (yerba mate) represents one of the most culturally widespread exposures, particularly in Argentina, Uruguay, Paraguay, and southern Brazil. Uruguay has the highest per capita consumption, estimated at 8–10 kg annually, followed by Argentina at approximately 5–6 kg and southern Brazil at 3–5 kg per year (Gawron-Gzella et al. 2021). Yerba mate is traditionally consumed as an aqueous infusion prepared by repeatedly adding near-boiling water to dried leaves and stemlets of *I. paraguariensis*. The beverage is typically consumed from a hollowed gourd through a metal straw known as a *bombilla*, a practice deeply embedded in regional cultural traditions (Figure 3). This distinctive mode of consumption frequently involves water temperatures exceeding 65°C–70°C and repeated intake throughout the day over many years or decades. Such chronic exposure to very hot beverages has prompted sustained epidemiological investigation into its potential association with cancers of the upper aerodigestive tract (Goldenberg 2002; Goldenberg et al. 2004).

The term *mate*, derived from the Quechua word for "cup", refers to the traditional vessel used for its consumption. Hot mate is predominantly consumed in Brazil, Argentina, and Uruguay, whereas cold preparations, commonly known as *tereré*, are widely consumed in Paraguay and parts of southern Brazil. Mate consumption has also expanded to other regions, including

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FIGURE 3 | Mate consumption and associated oral mucosal alterations. (A) Traditional preparation of yerba mate in a gourd using a metal straw (*bombilla*). (B) Dried and fragmented leaves and stemlets of *Ilex paraguariensis* used to prepare mate. (C) Solitary white keratotic patch on the lower lip vermilion, with a slightly irregular surface and relatively well-defined margins. (D) Hard palate showing multiple punctate erythematous papules and a focal central erythematous ulceration, compatible with thermal mucosal injury associated with hot mate consumption.

Lebanon, northern Israel, and, more recently, the United States, where it is often marketed in commercially packaged tea bags. Traditionally used by South American *gauchos* as a stimulant, yerba mate has more recently gained recognition as a nutraceutical beverage because of its high content of polyphenols and other bioactive compounds. These constituents have been associated with antioxidant, hypocholesterolemic, hepatoprotective, diuretic, and central nervous system stimulant properties (Heck and de Mejia 2007).

The IARC has classified the consumption of very hot beverages (> 65°C), including tea, coffee, and mate, as probably carcinogenic to humans (Group 2A) (IARC 2018a). Accordingly, the potential association between mate consumption and carcinogenesis has been investigated for more than five decades. A key unresolved question is whether this association is primarily attributable to thermal injury caused by repeated exposure to very hot liquids or to potentially carcinogenic constituents present in mate itself. In this context, previous studies have reported associations between mate consumption and cancer risk irrespective of infusion temperature. Consumption of more than 1 L of mate per day has been associated with higher odds of upper aerodigestive tract cancer than consumption of less than 1 L per day. Other studies have reported a significant adjusted association between mate consumption and oral/oropharyngeal cancer. A meta-analysis yielded a significant summary odds ratio of 2.11 (95% confidence interval: 1.39–3.19), with a population-attributable risk of 16% for mate consumption (Dasanayake et al. 2010; Mello et al. 2018).

Early epidemiological investigations into the potential association between mate consumption and cancers of the upper aerodigestive tract emerged in the late 20th century. A hospital-based case–control study conducted in Uruguay reported that heavy mate consumption was associated with an increased risk of tongue cancer, suggesting that the infusion might contribute to oral carcinogenesis beyond the well-established effects of tobacco and alcohol (Oreggia et al. 1991). Shortly thereafter, mate consumption was associated with an approximately twofold higher risk of cancers of the oral cavity, pharynx, and larynx in southern Brazil, even after adjustment for tobacco and alcohol use (Pintos et al. 1994). In the early 2000s, the discussion expanded through narrative and clinical reviews exploring potential biological mechanisms linking mate consumption to carcinogenesis. These reviews proposed that mate consumption may act as a risk factor for cancers of the oral cavity, oropharynx, larynx, and esophagus (Goldenberg 2002; Goldenberg et al. 2003).

Two main hypotheses have been proposed to explain the carcinogenicity of mate consumption: (i) repeated thermal injury to the mucosa caused by the consumption of very hot infusions; and (ii) exposure to potentially carcinogenic compounds (e.g., polycyclic aromatic hydrocarbons) present in processed leaves. These findings have contributed to increasing international awareness of mate consumption as a culturally embedded exposure potentially relevant to upper aerodigestive tract carcinogenesis in South America. In a case–control study conducted in Brazil and Argentina, the association with mate consumption was strongest for esophageal cancer, whereas the evidence for oral cavity cancer was less consistent (Szymańska et al. 2010). Moreover, a modest association between mate consumption and OSCC was observed in Uruguay, with evidence suggesting a synergistic interaction with tobacco and alcohol use (Deneo-Pellegrini et al. 2013). More recently, experimental and exposure-assessment studies have attempted to disentangle the relative contributions of chemical constituents and temperature.

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For example, the carcinogenic risk associated with mate consumption appears to be more plausibly attributable to the intake of very hot beverages than to exposure to polycyclic aromatic hydrocarbons alone, reinforcing the hypothesis that chronic thermal injury may play a central role in the observed epidemiological associations (Okaru et al. 2018).

Interestingly, although mate consumption may create conditions conducive to dysplastic changes in the oral mucosa and upper aerodigestive tract, it does not appear to produce a specific or pathognomonic OPMD clearly associated with the habit, unlike other culturally embedded risk factors. For instance, coca leaf chewing has been associated with characteristic lesions of the buccal mucosa, whereas RS is strongly associated with palatal keratosis. Nevertheless, isolated cases of palatal and labial keratotic lesions, sometimes accompanied by epithelial dysplasia, have been reported, particularly among individuals who habitually consume mate at near-boiling temperatures (Figure 3).

From a population perspective, the public health implications may be substantial because mate consumption is widespread and often begins in adolescence, continuing throughout adulthood. Even modest increases in individual risk could therefore have population-level relevance. However, the evidence specifically linking mate consumption to oral cavity cancer remains less consistent than that for esophageal and other upper aerodigestive tract cancers. Thus, mate consumption, particularly at high temperatures and over prolonged periods, should be considered a culturally embedded exposure of potential relevance to oral carcinogenesis, while recognizing the limitations of the current evidence. Future studies should apply the IARC framework based on the 10 key characteristics of human carcinogens to clarify the relative contributions of chronic thermal injury and potential chemical carcinogens associated with processing and preparation methods (IARC 2019; Smith et al. 2016).

5 | Charcoal-Grilled and Roasted Meat Consumption

The Southern Cone of South America is characterized by the frequent consumption of charcoal-grilled and roasted meats, a deeply rooted cultural practice. In Argentina, Uruguay, and southern Brazil, *asado* and related cooking practices represent both a dietary pattern and a central social tradition. Direct exposure of meat to open flames or hot charcoal promotes the formation and surface deposition of combustion-derived compounds with carcinogenic potential (Franco et al. 1989; Lee et al. 2016; Zheng and Lee 2009).

The IARC has classified processed meat as carcinogenic to humans (Group 1) and red meat as probably carcinogenic to humans (Group 2A) (0, 2018b). High-temperature cooking methods, including grilling and charcoal barbecuing, can generate polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic amines (HCAs) (Duedahl-Olesen and Ionas 2022; Oz et al. 2023). PAHs arise predominantly from incomplete combustion and may be deposited on the meat surface through smoke, whereas HCAs are formed through reactions involving amino acids, sugars, and creatine at high temperatures. Following metabolic activation, these compounds may induce DNA-adduct formation, mutations, and oxidative stress (IARC 2015, 2018b; Lee et al. 2016). However, most mechanistic evidence relates to gastrointestinal and systemic malignancies and does not establish a specific pathway for oral carcinogenesis (Bulanda and Janoszka 2022; Jeyakumar et al. 2017; Xu et al. 2014). Because oral contact during mastication is brief, any potential contribution to OSCC would more plausibly reflect cumulative dietary exposure and metabolic activation than prolonged direct mucosal contact. This mechanism, however, remains unproven in the oral mucosa.

Oral cancer-specific epidemiological evidence remains limited. A Brazilian case–control study reported an association between frequent consumption of charcoal-grilled meat and oral cancer (Franco et al. 1989). A meta-analysis of 13 observational studies, including 501,730 participants and 4104 cases of oral cavity or oropharyngeal cancer, found an association with processed meat consumption but not with total, red, or white meat consumption. An association was also observed in the South American subgroup, although this estimate was based on only three studies (Xu et al. 2014). Similarly, the Netherlands Cohort Study found an association between processed meat and oral cavity cancer but not between red meat and this outcome (Perloy et al. 2017). Higher red meat intake was associated with OSCC in Argentina, although cooking methods were not assessed separately (Secchi et al. 2015). More recently, smoked meat, but not grilled meat, remained significantly associated with oral cancer when different cooking methods were considered jointly (Bulanda et al. 2024).

Current evidence does not establish charcoal-grilled meat or *asado* as an independent risk factor for OSCC. The association appears more consistent for processed meat, whereas evidence specifically addressing charcoal grilling remains limited and inconsistent. Moreover, the potential contribution of *asado* is difficult to distinguish from broader dietary patterns and coexisting tobacco, alcohol, socioeconomic, and nutritional factors. Therefore, *asado* should be regarded as a culturally relevant, hypothesis-generating exposure rather than an established oral carcinogenic factor. Prospective multicenter studies should distinguish meat type from cooking method and assess consumption frequency, portion size, degree of doneness or charring, dietary patterns, and major carcinogenic co-exposures.

6 | Coca Leaf Chewing Habits

Coca leaf chewing is an ancestral practice deeply rooted in Andean cultures for more than two millennia and has traditionally served ritual, medicinal, and social purposes (Wilson et al. 2013). It is concentrated primarily in Bolivia and Peru and also occurs in parts of Colombia, northern Chile, and northwestern Argentina, particularly Salta and Jujuy, where it is practiced across diverse social and occupational groups (Figure 1) (Molina-Ávila et al. 2024).

The practice involves forming a bolus of dried coca leaves, known as *acullico*, which is commonly positioned in the posterior oral vestibule, gingivobuccal sulcus, or retromolar region (Figure 4). The bolus may remain in the mouth for prolonged periods, either statically or with intermittent repositioning.

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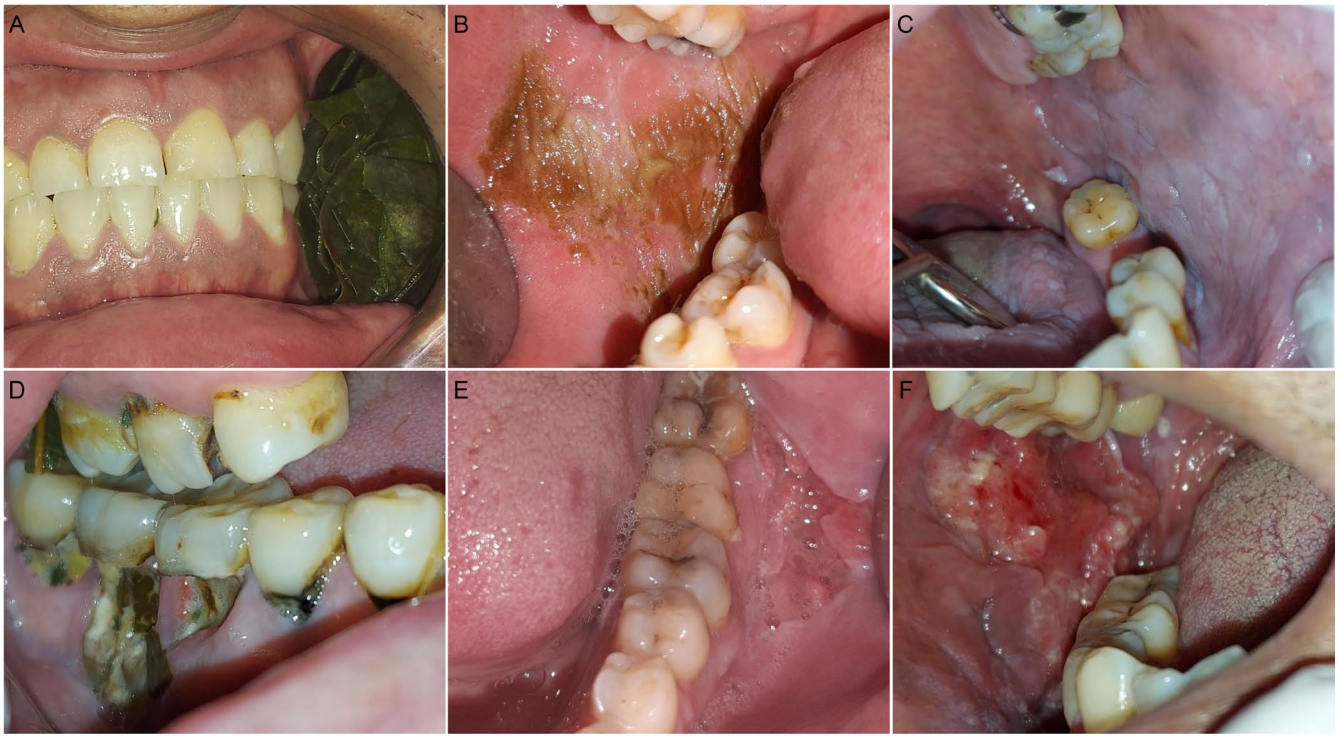

FIGURE 4 | Oral mucosal alterations associated with coca leaf chewing. (A) Coca leaves positioned in direct contact with the buccal mucosa during chewing. (B) Brownish extrinsic staining and keratotic changes at the habitual site of *acullico* placement. (C) Diffuse, poorly demarcated whitish keratotic plaque involving the posterior buccal mucosa and gingivobuccal region. (D) Multiple ulcerated lesions in the posterior mandibular gingivobuccal sulcus, corresponding to the site of chronic localized mucosal contact. (E) Oral squamous cell carcinoma involving the gingivobuccal complex in a patient with a history of coca leaf chewing. (F) Ulcerated and indurated oral squamous cell carcinoma affecting the buccal mucosa.

Many users repeatedly place it on the same side, resulting in localized and recurrent exposure of the oral mucosa. Alkaline substances, including lime, sodium bicarbonate, and traditional additives (e.g., llipta or yista), are commonly used to increase salivary pH and facilitate alkaloid extraction and permeation through the oral mucosa. Tobacco may also be incorporated into or used alongside the bolus. Because tobacco is an established oral carcinogen, its co-use represents an important potential confounder when evaluating the association between coca leaf chewing and OSCC.

Leaves of *Erythroxylum coca* contain several alkaloids, principally cocaine, as well as cinnamoylcocaine, tropacocaine, methylecgonine, and benzoylecgonine. During chewing, these compounds are progressively released into the saliva, while the combination of leaves, saliva, and alkaline additives creates a distinctive local chemical environment (Biondich and Joslin 2016; Borghelli et al. 1975). Chronic mechanical irritation caused by prolonged bolus placement and local chemical injury associated with the alkaline environment represents more plausible potential mechanisms. Nevertheless, their contribution to oral carcinogenesis remains hypothetical and has not been directly demonstrated.

Coca chewing has historically been associated with reactive oral mucosal alterations (Borghelli et al. 1975). More recent studies have explored its possible association with OSCC, particularly lesions involving the gingivobuccal complex and retromolar region (Molina-Ávila et al. 2020, 2022, 2024, 2026). This anatomical distribution differs from that commonly reported in most South American OSCC series, in which the tongue remains the predominant site of involvement (Gilligan et al. 2024; Louredo et al. 2023). This association may also be relevant to younger populations who adopt the practice early as part of their daily lifestyle (Gilligan et al. 2025).

The comparison with betel-quid chewing should be understood as behavioral and anatomical rather than chemical. Both practices involve prolonged and recurrent placement of a bolus at a preferential oral site, corresponding to the location of associated mucosal alterations and, in some cases, OSCC involving the gingivobuccal complex (Imran et al. 2025; Panta 2020; Zain et al. 1999). However, betel quid contains areca nut, an established human carcinogen, whereas coca leaves and their alkaloids have no comparable established carcinogenic classification. Evidence derived from betel-quid chewing therefore cannot be directly extrapolated to coca consumption.

A case series described clinicopathological mucosal alterations at the habitual site of *acullico* placement among individuals without reported tobacco or alcohol use. These findings support a possible relationship between prolonged localized exposure, chronic mechanical irritation, and oral mucosal injury (Molina-Ávila et al. 2022). More recently, a comparative cross-sectional study reported a higher frequency of oral mucosal alterations (e.g., oral leukoplakia) among coca chewers and documented OSCC involving the gingivobuccal complex at the self-reported habitual site of bolus placement (Molina-Ávila et al. 2026). Nevertheless, these observations do not establish causality. Larger independent multicenter studies should evaluate coca

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exposure separately from tobacco use and alkaline additives and assess the frequency, duration, laterality, and location of bolus placement. Mechanistic studies are also required to clarify the relative contributions of mechanical irritation, alkaline injury, environmental contaminants, nutritional factors, and other co-exposures.

7 | Palatal Lesions in Reverse Smokers

Reverse smoking (RS) is a tobacco-use practice in which the lit end of a cigarette or cigar is placed inside the oral cavity. The tobacco product is held between the teeth and lips, creating a seal through which smoke is partially expelled, while ash and residual smoke are directed inward and may be swallowed or inhaled (Alvarez Gómez et al. 2008). Unlike conventional smoking, in which exposure is more diffuse, RS directly exposes the palatal mucosa to intense heat and concentrated tobacco carcinogens. The World Health Organization (WHO) recognizes palatal lesions in reverse smokers as an OPMD (Warnakulasuriya et al. 2021). Several terms have been used in the literature, including *reverse-smoker's palate* and *palatal keratosis associated with reverse smoking* (Won and Clark 2022). However, the term *palatal lesions in reverse smokers* is used here in accordance with the WHO consensus nomenclature.

Although cases have been documented since the 1930s, the first clinicopathological description in Caribbean populations was published in 1964 (Quigley Jr. et al. 1964). Subsequent studies from Andhra Pradesh in southeastern India reported a high prevalence of RS with *chutta* and a possible association with OSCC (Pindborg et al. 1971). Additional studies reported associations with palatal lesions, histopathological alterations, and malignant transformation, and increased mortality (Gavarasana and Susarla 1989; Gupta et al. 1984; Hedin et al. 1992; Mehta et al. 1972; Ramulu and Reddy 1972; Reddy 1974; van der Eb et al. 1993). RS has also been documented among Filipino women (Mercado-Ortiz et al. 1996).

In South America, RS has been documented along Colombia's Caribbean coast, particularly in the Department of Sucre (Alvarez Gómez et al. 2008). A household-based study reported palatal lesions in 15% of individuals practicing RS and OSCC in 12.5% (Alvarez Gómez et al. 2008). In this region, the tobacco product is commonly a handmade cigar known as *calilla*, prepared from sun-dried black tobacco (*Nicotiana tabacum*), rolled around a thin stick, and bound with yucca starch. RS is also deeply rooted in rural, coastal, and fishing communities in Venezuela, where both manufactured cigarettes and traditional handmade cigars are used (Gamboa and Villarroel-Dorrego 2013). Of note, with the exception of reports from Sardinia, Italy, the practice has been documented predominantly among women living in rural areas, particularly those facing socioeconomic disadvantage, limited educational opportunities, and restricted access to healthcare services (Angulo Quiñónez and López-Ulloa 2019; Hogewind et al. 1989; Mercado-Ortiz et al. 1996).

Several factors have been associated with the adoption and persistence of RS. Women may have initially used this practice to conceal tobacco consumption from relatives, prevent tobacco from being extinguished during domestic or fishing activities, or avoid ash falling onto infants or clothing (Bharath et al. 2015; Gupta et al. 1984). In Colombian communities, reported motivations have included pleasure, the sensation of internal warmth, avoidance of conventional smoking, and intergenerational cultural transmission (Alvarez Gómez et al. 2008). Beliefs that tobacco may relieve toothache or repel mosquitoes may further reinforce the practice. Consequently, RS has become integrated into the cultural identity of some rural communities (Harini et al. 2016).

RS causes combined thermal and chemical injury. Thermal injury results from the proximity of the burning end to the palatal mucosa, whereas chemical exposure results from the retention of tobacco compounds and carcinogens within the oral cavity. The internal temperature of a cigar may reach 760°C, with a mean of 663°C, while external temperatures average 464°C. Temperatures of up to 120°C within the oral cavity and 64°C at the palatal mucosa have also been reported (Quigley Jr. et al. 1964). Although tobacco-specific nitrosamines have not been quantified in products used by the Colombian and Venezuelan populations studied, analyses of Indian *chutta* have identified high concentrations of N′-nitrosonornicotine, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone, and N′-nitrosoanatabine (Pakhale and Maru 1998). Individual smoking episodes may last up to 18 min, with a reported mean duration of 7 min and 42 s (Alvarez Gómez et al. 2008; Quigley Jr. et al. 1964). Repeated daily use, commonly involving 2–4 cigarettes, therefore results in prolonged and recurrent exposure of the same palatal area (Bharath et al. 2015).

Clinical changes associated with RS include melanosis, leukoedema, central atrophy, and white or red patches (Figure 5). The WHO characterizes palatal lesions in reverse smokers as white and/or red patches affecting the hard palate, frequently accompanied by tobacco staining (Warnakulasuriya et al. 2021). Additional manifestations include papules, fissuring, umbilication of minor salivary gland duct openings, and ulceration (Dharmavaram et al. 2016). Although the hard palate is predominantly affected, extension to the soft palate and changes involving the tongue, buccal mucosa, and gingiva have also been described (Alvarez Gómez et al. 2008; Gamboa and Villarroel-Dorrego 2013). The term *nicotinic stomatitis* should not be used synonymously because it refers to the generally benign palatal alteration associated with conventional smoking and is clinically and pathologically distinct from palatal lesions related to RS. Table 1 summarizes the clinical and histopathological manifestations and their severity.

Histopathological and cytological findings include inflammatory cells within the keratin layer, Candida-associated alterations, and koilocytosis (Alvarez Gómez et al. 2008). Altered p53 expression intensity and suprabasal localization have also been reported (Gamboa and Villarroel-Dorrego 2013). However, these molecular findings are preliminary and require confirmation in larger and independent studies.

The strong cultural roots of RS may limit the effectiveness of conventional cessation strategies. Culturally adapted, community-based interventions involving mothers, older

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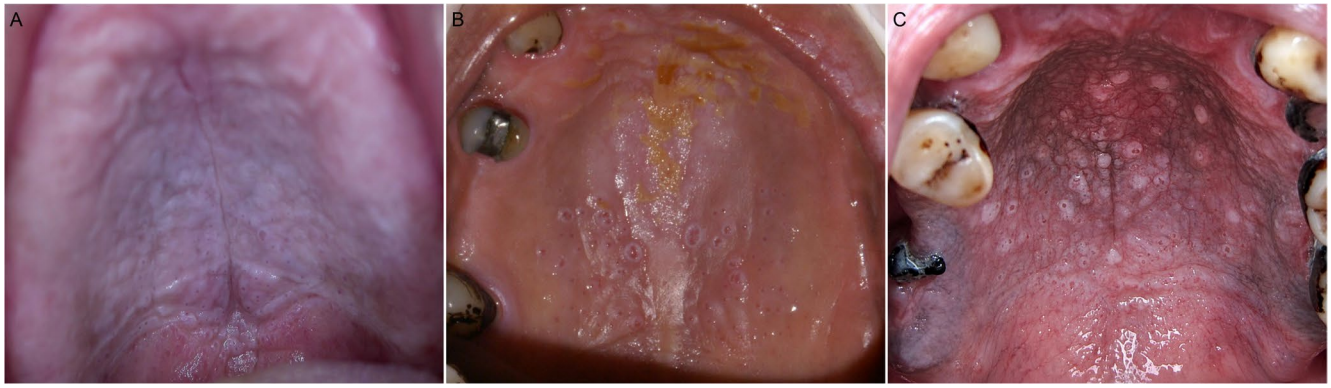

FIGURE 5 | Palatal lesions in reverse smokers. (A) Mild palatal mucosal changes characterized by subtle erythematous and papular areas. (B) Palatal lesions comprising white plaques, papules, umbilicated papules, and focal erythematous areas. (C) Severe palatal changes associated with reverse smoking, characterized by multiple white plaques, papules, umbilicated papules, erythematous areas, and diffuse melanosis.

TABLE 1 | Clinical and histopathological grading of palatal lesions in reverse smokers.

Grade	Severity	Clinical appearance	Histopathological features[a]
0	Normal	Healthy oral mucosa	Healthy oral mucosa
1	Mild changes	Focal or diffuse involvement of the oral mucosa, including diffuse whitening of the palatal mucosa, dark brown or brown-grayish macules with defined and irregular borders, and focal areas clinically devoid of melanin pigmentation, often surrounded by hyperpigmentation	Melanin deposits in the basal layer of the epithelium and hyperkeratinization
2	Moderate changes	Elevated rounded white papules, usually < 1 cm, with a smooth surface; white plaques with smooth or rough surfaces, defined and irregular borders, not removable by scraping, and sometimes associated with tobacco-related yellow pigmentation. On the tongue, white areas may be separated by fissures	Slight to moderate epithelial hyperplasia, hyperorthokeratosis or hyperparakeratosis, "Christmas tree" hyperkeratosis, acanthosis, and chronic inflammatory cell infiltrate. Squamous metaplasia of minor salivary gland ducts may be observed. In depigmented areas, disappearance of rete pegs and dysplastic changes may occur
3	Severe changes	White or reddish papules located on the hard and/or soft palate, with an invaginated red central point; well-defined red flat lesions of the palatal mucosa with smooth surface and irregular borders, clinically indistinguishable from erythroplakia; crater-like ulcerations with fibrin deposits, often surrounded by keratinization. These alterations may coexist with mild or moderate features	Hyperorthokeratosis or hyperparakeratosis and epithelial dysplasia. In red areas, atrophic epithelium and, in some cases, epithelial dysplasia may be present
4	Probably malignant	Exophytic and/or ulcerated lesions involving the oral mucosa, clinically suspicious for malignancy	Oral squamous cell carcinoma

[a]The five-grade framework was adapted from Ramulu et al. (1973). The clinical and histopathological features were compiled from Mehta et al. (1977), Alvarez Gómez et al. (2008), Bharath et al. (2015), and Dharmavaram et al. (2016).

women, local leaders, and healthcare workers may be more appropriate in communities where these individuals contribute to the social transmission of the practice (Harini et al. 2016). Repeated counseling integrated into rural health programs may also support cessation efforts (Jayakrishnan et al. 2013). In a study of 101 reverse smokers in rural Andhra Pradesh, monthly follow-up and intensive individualized communication over 12 months resulted in complete cessation among 24% of participants, while 27% shifted to conventional smoking (Mehta et al. 1977).

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Evidence concerning palatal lesions in reverse smokers remains limited by underreporting, underdiagnosis, and inadequate surveillance. The absence of specific ICD-10 and ICD-11 codes, limited clinical awareness, barriers to habit disclosure, and restricted access to healthcare in endemic regions may contribute to delayed diagnosis. Important gaps remain regarding malignant transformation rates, co-exposures, molecular alterations, and intervention effectiveness. Longitudinal studies, mechanistic investigations, and dedicated epidemiological registries are therefore needed, particularly in Colombia and Venezuela.

8 | Alcohol Consumption and Other Beverages

Alcohol consumption is an established risk factor for OSCC, with risk increasing according to the intensity and duration of exposure (Aswathi et al. 2026; IARC 2012). Ethanol is metabolized to acetaldehyde, a genotoxic compound capable of inducing DNA damage (IARC 2012). Alcohol and tobacco frequently occur as co-exposures and have a synergistic effect on OSCC risk (Mello et al. 2019; Szymańska et al. 2011).

In South America, this relationship is particularly relevant because of the consumption of regionally prevalent distilled beverages. In Brazil, the historical production and cultural incorporation of sugarcane-derived spirits, particularly *cachaça*, have contributed to the persistence of alcohol consumption as a relevant regional exposure (Martins et al. 2024). *Cachaça* has been associated with oral cancer across anatomical sites, whereas an association with wine was particularly evident for tongue cancer (Franco et al. 1989). A Brazilian case–control study also found that risks for mouth cancer were highest for hard liquor and *cachaça* at equivalent levels of lifetime ethanol exposure, although increased risks persisted across beverage types with continued consumption (Schlecht et al. 2001). These findings suggest that beverage type and drinking patterns may influence the magnitude of risk, while cumulative ethanol exposure remains central. Accordingly, regionally prevalent spirits, including *cachaça* in Brazil, *aguardiente* in Colombia, and *ron* in Venezuela, should be regarded as culturally relevant patterns of alcohol exposure rather than distinct oral carcinogens.

Other region-specific beverage practices remain insufficiently investigated. For example, the consumption of very hot coffee has been reported in populations from Puerto Rico and Colombia, with associations described for several upper aerodigestive tract malignancies, although evidence specific to oral carcinogenesis remains inconsistent (Martinez 1969; Restrepo et al. 1989). Further regional studies should assess beverage type, ethanol dose, drinking pattern, temperature, and relevant co-exposures.

9 | Future Directions

Future studies should adopt a standardized South American questionnaire with core and exposure-specific modules. For each practice, the instrument should record age at initiation, frequency, duration, cumulative exposure, product composition, preparation method, anatomical site and laterality of contact, and temperature when applicable. Tobacco exposure should be quantified by type, intensity, duration, and cumulative use, while alcohol consumption should be documented according to beverage type, frequency, amount, and cumulative ethanol exposure. The timing and concurrent use of these exposures should also be recorded.

Confounding represents a central challenge because culturally embedded practices may cluster with tobacco and alcohol use, socioeconomic disadvantage, poor diet, nutritional deficiencies, inadequate oral hygiene, occupational exposures, and limited access to healthcare. Future studies should therefore include never-smokers and non-drinkers whenever possible, together with appropriately matched unexposed controls. Multivariable and stratified analyses, interaction models, and sensitivity analyses excluding participants with major conventional risk factors would help determine whether these practices act independently, synergistically, or as markers of broader social and behavioral profiles (Martínez-Ramírez et al. 2024).

A prospective multicenter South American registry should be established using harmonized definitions, data-collection procedures, and diagnostic criteria. An associated biobank could include clinical photographs, saliva, histopathological specimens, and fresh or archived tissue from exposed individuals, patients with OPMDs, and patients with OSCC. Standardized collection and storage protocols would support independent validation and facilitate studies of DNA damage, genomic and immunohistochemical alterations, microbiome profiles, and exposure-specific molecular signatures.

Research priorities should reflect the strength of evidence for each exposure. For practices supported mainly by clinical observations or biological plausibility, such as coca leaf chewing, hot mate consumption, and charcoal-grilled meat intake, adequately powered epidemiological studies should precede causal claims. For reverse smoking and chimó use, longitudinal studies should quantify dose–response relationships, malignant transformation, and interactions with tobacco and alcohol. Mechanistic studies should clarify whether thermal injury, alkaline or mechanical irritation, and exposure to tobacco-related or combustion-derived carcinogens contribute directly to oral carcinogenesis. Public health interventions should be developed alongside research. As such, community-based education, culturally adapted cessation strategies, and professional training may improve habit disclosure, recognition of associated oral lesions, and timely referral, particularly in rural and underserved populations. Coordinated regional efforts integrating epidemiology, oral medicine, pathology, molecular research, and public health are needed to improve risk stratification and develop prevention strategies adapted to South American populations. Table 2 provides a summary of the different risk factors analyzed, detailing their most r elevant characteristics.

10 | Conclusions

OSCC in South America occurs within heterogeneous sociocultural contexts that include region-specific exposures not fully captured by conventional risk models. Although thermal, chemical, and mechanical injury provide biologically plausible links to oral carcinogenesis, the strength of the evidence varies substantially

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TABLE 2 | Qualitative appraisal of culturally embedded and regionally prevalent exposures potentially associated with oral squamous cell carcinoma in South America.

Exposure	Associated oral findings	Typical geographic distribution	IARC/international recognition	Included in oral cancer prevention campaigns	Epidemiological evidence in South America	Biological plausibility	Strength of evidence[a]	Overall interpretation
Chimó smokeless tobacco paste[b]	Localized mucosal keratosis, gingival alterations, and leukoplakia	Venezuela	Smokeless tobacco is carcinogenic to humans (Group 1); chimó has not been evaluated separately	Limited	Moderate	Strong	Moderate	Probable regional risk factor
Hot mate consumption[c]	No pathognomonic oral lesion; occasional palatal or labial keratosis; chronic thermal injury is the main proposed local mechanism when consumed at very high temperatures	Argentina, Uruguay, Paraguay, and southern Brazil	Beverages consumed above 65°C are probably carcinogenic to humans (Group 2A), based predominantly on evidence for esophageal cancer; mate not consumed very hot is not classifiable as to its carcinogenicity to humans	Rarely	Limited	Moderate	Limited	Plausible thermal exposure, but OSCC-specific evidence remains limited
Charcoal-grilled meat/*asado*[d]	No specific oral lesion; potential exposure to polycyclic aromatic hydrocarbons and heterocyclic aromatic amines generated during high-temperature cooking	Argentina, Uruguay, southern Brazil, and Chile	Processed meat is carcinogenic to humans (Group 1), and red meat is probably carcinogenic to humans (Group 2A); *asado* and charcoal grilling have not been evaluated as distinct carcinogenic exposures	No	Limited	Moderate	Limited	Hypothesis-generating regional exposure
Coca leaf chewing	Gingivobuccal keratosis, leukoedema-like alterations, and localized mucosal thickening; OSCC has been reported at habitual sites of bolus placement	Bolivia, Peru, northern Argentina, and other Andean regions	Coca leaf chewing has not been evaluated by IARC as a specific oral carcinogenic exposure	No	Limited	Moderate	Limited	Emerging hypothesis requiring further investigation
Reverse smoking	Palatal keratosis, papules, umbilicated papules, red areas, ulcerations, and palatal OSCC	Caribbean coast of Colombia and coastal and rural regions of Venezuela	Tobacco smoking is carcinogenic to humans (Group 1); reverse-smoker's palate is recognized as an OPMD	Rarely included in targeted campaigns	Moderate	Strong	Strong	Most strongly supported region-specific tobacco practice reviewed

(Continues)

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TABLE 2 | (Continued)

Exposure	Associated oral findings	Typical geographic distribution	IARC/international recognition	Included in oral cancer prevention campaigns	Epidemiological evidence in South America	Biological plausibility	Strength of evidence[a]	Overall interpretation
Alcohol consumption, including regional distilled beverages[e]	No pathognomonic oral lesion	Throughout South America	Alcoholic beverages are carcinogenic to humans (Group 1), with sufficient evidence for oral cavity cancer	Generally included	Strong	Strong	Strong	Established OSCC risk factor; beverage-specific effects remain uncertain

Abbreviations: IARC, International Agency for Research on Cancer; OPMD, oral potentially malignant disorders; OSCC, oral squamous cell carcinoma.

[a]Strength of evidence was qualitatively classified as strong, moderate, or limited according to the number and consistency of studies, representation of South American populations, adjustment for major confounders, mechanistic support, and international carcinogenic recognition. IARC classifications refer to the evaluated agents or exposures and should not be directly extrapolated to individual regional practices.

[b]For *chimó*, the classification applies to smokeless tobacco as a general category.

[c]For mate consumption, the classification applies to beverages consumed at very high temperatures and is based predominantly on evidence for esophageal cancer.

[d]For *asado*, the classifications apply to red and processed meat, not specifically to charcoal grilling.

[e]For alcohol, the evidence is strong for alcoholic beverage consumption, whereas differences among specific regional beverages remain uncertain.

and remains limited for several practices. Systematic recognition and documentation of these exposures may improve risk assessment, early identification of OPMDs, and culturally appropriate prevention. Coordinated regional research is needed to clarify their independent and combined contributions and translate the findings into context-specific cancer control strategies.

Author Contributions

Ignacio Molina-Ávila: conceptualization, investigation, methodology, validation, writing – original draft, writing – review and editing, resources. **José Alcides Almeida de Arruda:** conceptualization, writing – review and editing, visualization, validation, methodology, software, formal analysis, data curation, funding acquisition, supervision, resources. **René Panico:** conceptualization, investigation, methodology, supervision. **Gloria Jeanethe Álvarez Gómez:** conceptualization, investigation, writing – original draft, methodology, validation, visualization, writing – review and editing, formal analysis, data curation, supervision. **Eduardo Piemonte:** conceptualization, writing – original draft, visualization, writing – review and editing, formal analysis, supervision. **Leonardo Amaral dos Reis:** conceptualization, funding acquisition, methodology, validation, visualization, writing – review and editing, software, formal analysis, data curation, supervision, resources. **Saman Warnakulasuriya:** validation, visualization, formal analysis, writing – review and editing, supervision, resources. **Gerardo Gilligan:** conceptualization, investigation, funding acquisition, writing – original draft, methodology, validation, writing – review and editing, visualization, project administration, data curation, supervision, resources. **Ronell Bologna-Molina:** conceptualization, writing – original draft, validation, visualization, writing – review and editing, formal analysis, supervision, resources. **Bruno Augusto Benevenuto de Andrade:** validation, visualization, writing – review and editing, formal analysis, supervision, resources. **Mariana Villarroel-Dorrego:** conceptualization, investigation, writing – original draft, methodology, validation, visualization, software, formal analysis, data curation, supervision, writing – review and editing.

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Ethics Statement

Written informed consent was obtained from all patients whose clinical photographs are included in this article, including authorization for the publication of their anonymized images for scientific and educational purposes.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

Data sharing was not applicable to this article as no datasets were generated or analysed during this study.

Peer Review

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