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Association between coca *(Erythroxylum coca)* chewing habit and oral squamous cell carcinoma: a case-control study from Argentina

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Objective. Previous isolated reports have hypothesized that chewing coca leaves, a pre-Columbian tradition found in certain regions of South America, may be associated with the development of oral squamous cell carcinoma (OSCC). Coca chewing (CC) is a habit that shares many characteristics with the well-known practice of betel chewing observed in Asia. The aim of this study is to analyze the association between CC and OSCC among patients who attended the Señor del Milagro Hospital in Salta, Argentina.
Study Design. A case-control study was conducted from 2013 to 2018. For each case of OSCC, three healthy control patients were included. Odds ratios were calculated to compare demographics, concurrent oral conditions, and other classical risk factors for OSCC.
Results. A total of 62 cases and 180 controls were included, adjusted for sex and age. OSCC was significantly associated with tobacco use (27.4% vs 9.4%, $P = .001$), CC (62.9% vs 32.2%, $P < .001$), and poor oral condition (81.1% vs 67.7%, $P = .02$). In the multivariate analysis, smoking (OR = 2.77, 95% CI 1.23-6.25, $P = .0139$), CC (OR = 2.98, 95% CI 1.58-5.63, $P = .0007$), and poor oral condition (OR = 3.1, 95% CI 1.62-5.85, $P = .0006$) remained independently associated with OSCC development.
Conclusions. Chewing coca leaves could be considered a risk factor for oral cancer in a subset of Argentinean patients. Further studies are necessary to validate our findings and to elucidate the underlying pathways linking this habit to oral carcinogenesis. (Oral Surg Oral Med Oral Pathol Oral Radiol 2024;000:1−10)

Malignancies represent the second leading cause of death worldwide.[1] Oral cancer ranks 16th in both incidence and mortality globally. Approximately 90% of oral malignancies are classified as oral squamous cell carcinoma (OSCC).[2] Previous data indicate that only 15% of cases are diagnosed at early stages.[3,4] In Argentina, around 3,000 new cases of oral cancer are diagnosed annually, resulting in approximately 800 deaths, with a 5-year survival rate of 37%.[4,5] OSCC is a multifactorial disease. Classical risk factors associated with OSCC include tobacco and alcohol consumption, as well as betel quid usage. However, other noncanonical factors may also contribute to OSCC development, such as low consumption of fruits and vegetables, chronic inflammation, and oral dysbiosis.[6,7]

Various geographical variations in the epidemiological and clinical profile of OSCC across Latin America have been identified. Notably, Salta, a province in northern Argentina, exhibits high consumption of coca leaves (*Erythroxylum coca*) and demonstrates a specific association with a high frequency of OSCC occurring in the gingivobuccal complex (GBC).[8] The coca bush, belonging to the genus *Erythroxylum*, is original to Central and South America. The plant is characterized by its large, dark green leaves with an elliptical shape and sharp apex. Coca leaves have historically been promoted as a dietary supplement to address nutritional deficiencies among Andean populations.[9] Approximately 18 different alkaloids can be found in coca leaves, including cinnamoylcocaine, tropacocaine, methylecgonine, and benzoylecgonine (Figure 1).

Coca-chewing (CC), also known as *coqueo*, is an ancient practice still prevalent among approximately 4 million individuals in Bolivia, Peru, and Northern Argentina.[10,11] CC has its roots in pre-Columbian indigenous populations. For example, the *Llullaillaco mummies*, consisting of 3 children discovered entombed within Llullaillaco Volcano in northern Argentina, were possibly sacrificed in an Inca ritual. During the radiological examination of the mummy known as "the Maiden", a coca quid was discovered within her mouth, clenched between her teeth and the buccal mucosa, indicating her ingestion of coca in her final moments. This archaeological finding highlights the ancestral significance of CC in Northern Argentina (Figure 2).[12]

Statement of Clinical Relevance

Chewing coca is a common habit found in South America. This study shows for the first time an etiological association between this ancestral tradition and oral squamous cell carcinoma development.

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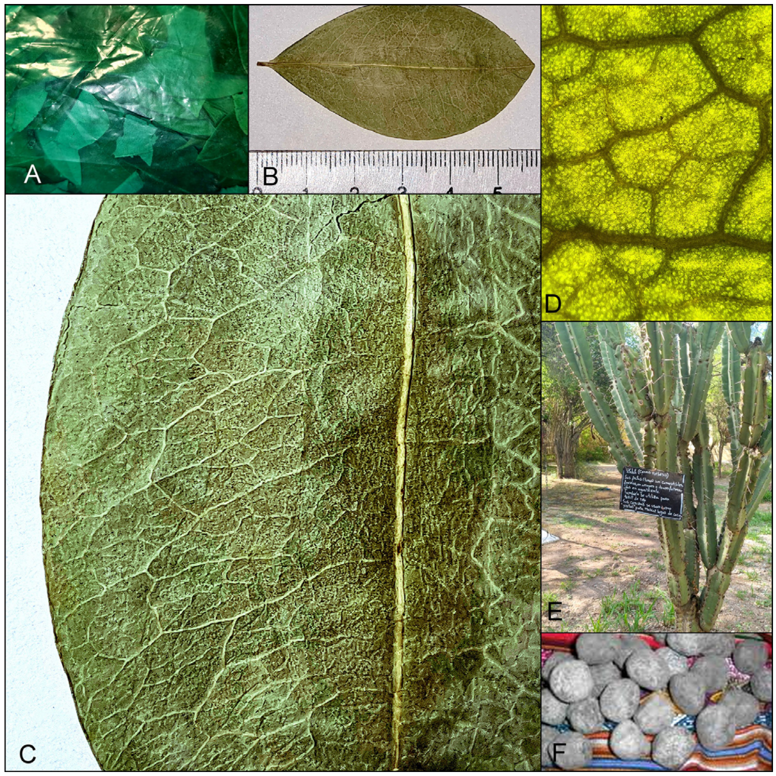

Fig. 1. A, Coca leaves for human consumption, packaged in small green bags or containers to prevent desiccation and maintain humidity, commonly found in northern Argentina, Bolivia, and Peru. B, Coca leaf, typically measuring 5 to 6 cm in size, with each acullico composed of approximately 20 to 25 leaves squeezed and placed at the bottom of the vestibule and gingivobuccal complex. C, Coca leaf (*Erythroxylum coca*) exhibiting large, dark green elliptical leaves with a sharp apex. D, Coca leaf observed under an optical microscope (10x), demonstrating surface irregularity and micro-roughness of the follicular cuticle. E, Cactus "ucle" (*cereus forbesii*), a fleshy perennial shrub found in central and northern regions of Argentina, with its ashes used as yista stones added to the acullico during coqueo. Photograph taken in San Marcos Sierra, Córdoba, Argentina. F, Yista or Llista stones, composed of ashes and other components such as bicarbonate, commonly added to the acullico during coqueo.

Coqueo involves placing coca leaves, commonly referred to as *acullico*, between the buccal mucosa, the retromolar pad, and the dental surfaces of the posterior region. *Acullico* may also contain baking soda, sodium, and tree ashes (*yista, llista*), and typically lasts for approximately 3 to 6 hours per day. Each *acullico* typically weighs between 3 to 6 grams[13] (Figure 1). Pre-Columbian natives believed that coca consumption could induce a stimulant effect and provide health benefits.[14] Coca leaves are often chewed along with yista, aiding in the extraction of cocaine, its primary active compound. When the acullico is chewed, coca juices are swallowed, resulting in measurable levels of plasmatic cocaine.[15,16] Habitual CC produces plasmatic cocaine levels within a similar range to those experienced by users of processed cocaine. However, this is not accompanied by the negative signs of addiction associated with chronic cocaine consumption, as plasmatic levels peak after approximately 60 minutes and gradually decrease, avoiding drastic changes in brain chemistry.[12,16,17]

South America harbours diverse traditions that vary among different cultures and population idiosyncrasies. Some of these traditions have been analyzed as particular risk factors for OSCC, such as reverse smoking or chimó chewing in Venezuela or Colombia, mate drinking in Uruguay and Argentina, etc.[8,18-20] Coqueo has been previously hypothesized as a noncommon risk factor for OSCC in Latin America.[8,10,14] Furthermore, the high frequency of GBC-OSCC in coca-chewers, and the resemblance of this practice to betel chewing often described in Asia, have led to the hypothesis that this tradition could be associated with the development of OSCC.[10,21] Due to the limited number of epidemiological studies linking CC and OSCC, the aim of this study was to investigate the association between *coqueo* or CC and OSCC among patients who sought care at the Señor del Milagro Hospital in Salta, Argentina.

Materials and Methods

A prospective case-control study was performed in the Oral Medicine Service of the Señor del Milagro

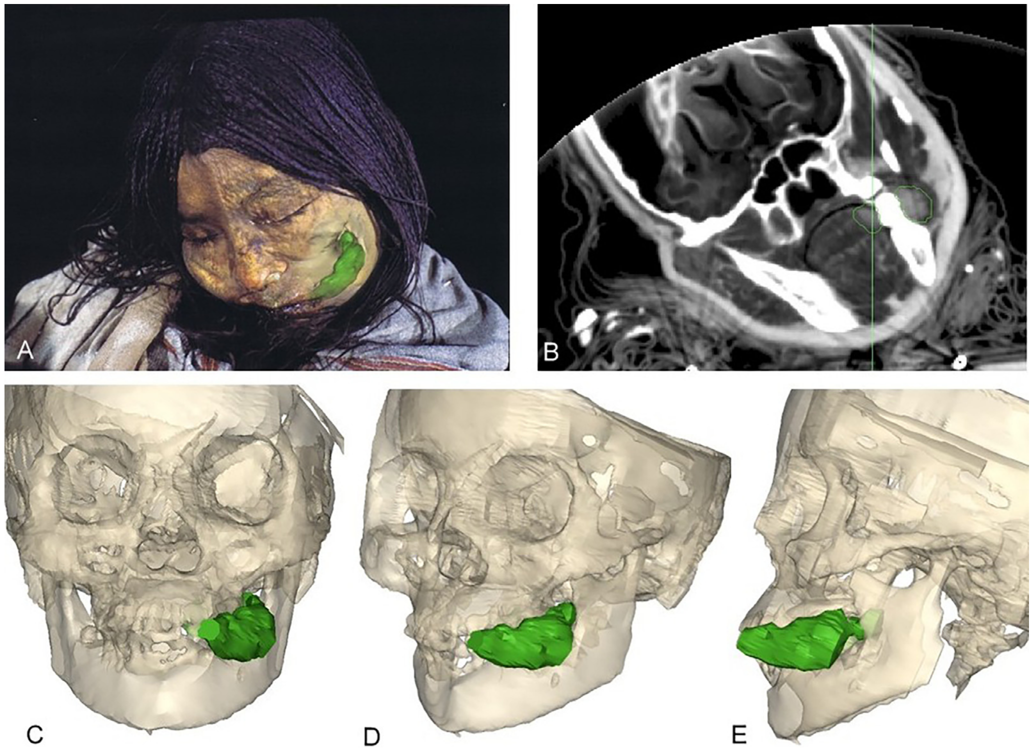

Fig. 2. A, "The Maiden" - Mummies of Llullaillaco. B, The CT Scan and three-dimensional reconstruction reveal the acullico (coca leaves) inside the girl's mouth, depicted in green, clenched between the teeth and the left buccal mucosa. C-D-E, Tomographic sections obtained through multiplanar reconstruction of the mummy, revealing the presence of the acuyico inside the oral cavity, highlighted in green. Obtained from "Wilson et al. Archaeological, radiological, and biological evidence offer insight into Inca child sacrifice; //doi.org/10.1073/pnas.1305117110." This figure was re-designed and provided by Chiara Villa, University of Copenhagen, who authorized its use in this publication (Supplementary material).

Hospital, Salta, Argentina (from July 2013 to December 2018).

Inclusion criteria. The case group comprised individuals diagnosed with primary OSCC affecting the tongue, GBC, or floor of the mouth, confirmed by histopathology. The control group consisted of patients without any anomalies or lesions in the oral mucosa. These patients were recruited during early detection campaigns for oral cancer conducted at the Señor del Milagro Hospital.

Exclusion criteria. Individuals diagnosed with oropharyngeal squamous cell carcinoma, OSCC affecting the lips and palate, and second primary OSCC were excluded from the study. Additionally, other histological subtypes of oral malignancies, such as neoplasms of the minor salivary glands, melanoma, lymphoma, metastatic tumors, and sarcomas, were also excluded.

A nonprobabilistic convenience sampling method was utilized. A minimum sample size of 59 cases and 175 controls was calculated, assuming a prevalence of exposure to the CC habit of 13%, a power of 80%, and a confidence level of 95%. The cases were matched in a 3:1 ratio and adjusted for age (±5 years) and sex. Clinico-epidemiological data were retrieved from clinical records, with patient identities protected through codification. Sociodemographic data (age, sex) and clinical variables (poor oral condition, denture use, anatomical site) were also recorded. All patients underwent examination by 2 calibrated Oral Medicine specialists (IM, JMP).

Risk factor records (smoking, alcohol consumption, CC) were collected in a binary manner (yes/no), considering it positive only when the habit was daily, regardless of the amount consumed daily. The variable "poor oral condition" was deemed present when patients exhibited visible biofilm with severe periodontal disease and/or extensive dental caries necessitating dental extraction. Denture use was considered positive when patients had been removable denture users for at least 10 years.

The anatomical location of tumors was documented. OSCC involving the GBC, as described above, was identified when the tumor affected the posterior area of the buccal mucosa, the vestibular sulcus, the adjacent buccal gingiva, and the retromolar pad.[22]

Statistical analysis

Qualitative variables were presented as frequencies and percentages, while quantitative variables were expressed as means and standard deviations or as median and interquartile range, as appropriate. Quantitative variables were compared using the *t* test or Mann−Whitney test, and qualitative variables were compared using the chi-square test or Fisher's exact test. Multivariate logistic regression models were also employed, with the OSCC variable as the dependent variable, to calculate odds ratios. A *P* value < .05 was considered statistically significant. Data analysis was conducted using the Epi Info™ statistical software.

The research protocol for this study was approved by the Teaching, Ethics, and Research Investigation Committee of the Señor del Milagro Hospital, Salta, Argentina (Protocol Number 47771, Exp 0100134-47771/2023-0).

RESULTS

A total of 242 patients (62 cases and 180 controls), with a mean age of 58 years old (SD±14.4), were included in the study. Among them, 149 (61.6%) were males and 93 (38.4%) were females. Smoking was reported by 34 individuals (14%), alcohol consumption by 40 (16.5%), and CC by 97 (40%) patients. Poor oral conditions were observed in 171 patients (70%) and 105 (43%) were denture users. Table I provides an overview of the socio-demographic characteristics of the overall group.

OSCC patients were more frequently smokers (27.4% vs 9.4%, *P* = .001), coca chewers (62.9% vs 32.2%, *P* < .001), and presented with poor oral conditions (81.1% vs 67.7%, *P* = .02) compared to the control group, with significant statistical differences (Table II). Figure 3 illustrates the differences in CC between both groups. In the multivariate analysis (logistic regression), smoking (OR = 2.77, 95% CI 1.23-6.25, *P* = .0139), CC (OR = 2.98, 95% CI 1.58-5.63, *P* = .0007), and poor oral condition (OR = 3.1, 95% CI 1.62-5.85, *P* = .0006) remained independently associated with OSCC development (Table III).

Table I. Demographic and clinical features

Variable	*Category*	*N (%)*
Total		242
Age (years)		58
Age range		(47-73)
Sex	Males	149 (61.6)
	Females	63 (38.4)
Smokers	Yes	34 (14)
	No	208 (86)
Drinkers	Yes	40 (16.5)
	No	202 (83.5)
Coca chewing	Yes	97 (40.1)
	No	145 (59.9)
Denture wearing	Yes	105 (43.4)
	No	137 (56.6)
Poor oral condition	Yes	171 (70)
	No	71 (30)
OSCC	Yes	62 (25.6)
	No	180 (74.4)

OSCC, oral squamous cell carcinoma.

In the stratified analysis of risk factors according to CC status, neither tobacco and alcohol consumption nor poor oral condition showed significance in the non-CC group (bivariate analysis; $\chi 2$). However, among individuals who practised CC, tobacco (OR = 2.7, 95% CI 1-7, *P* = .039) and poor oral health (OR = 4.4, 95% CI 1.8-10.7, *P* = .0006) exhibited statistically significant differences. In the multivariate analysis using logistic regression, the group of individuals who were not coca chewers showed no association with the three aforementioned risk factors. Conversely, in the CC group, tobacco (OR = 4.1, 95% CI 1.2-13.1, *P* = .018) and poor oral condition (OR = 6.6, 95% CI 2.3-18.8, *P* = .0003) were directly associated with statistical significance, while alcohol exhibited an inverse association (OR = 0.26, 95% CI 0.08-0.9, *P* = .035) (Table IV).

The GBC was the primary anatomical location of OSCC (*n* = 36), followed by the lateral tongue (*n* = 19) and the floor of the mouth (*n* = 7). OSCC associated with CC were more frequently located on the GBC compared to OSCC not related to the CC habit (*P* = .004) (Table V). Figure 4 depicts cases of OSCC associated with the CC habit and the high frequency of GBC location.

DISCUSSION

Coca leaves have been traditionally used by pre-Columbian indigenous populations, primarily through chewing, as part of religious ceremonies by the Inca, and for medicinal purposes.[11,16,23,24] In our setting, although *coqueo* is associated with certain professions, (such as long-distance bus drivers, who use it as an antisleeping agent), its recreational use is the most common. In the present study, the overall frequency of patients who chewed coca was 40%. In Peru, the National Institute of Statistics and Informatics reported a consumption of 3.1 kg of coca leaf per capita annually in 2013.[25] Oliva et al.[26] investigated the use of medicinal herbs in the suburbs and peri-urban neighbourhoods of Salta, Argentina, revealing that 53.8% of the surveyed households have a family member who engages in the practice of CC. These rates demonstrate that despite being an ancestral tradition, CC in this region of Latin America remains prevalent and continues to be a frequent habit.

There is a dearth of research investigating CC and its potential role in oral carcinogenesis. Previous

Table II. Bivariate analysis of risk factors between OSCC and control

Variable	*OSCC (n= 62 [%])*	*Control (n= 180 [%])*	*OR*[‡]	*CI 95%*	*P value*
Median age (±SD)	58.5 (14.8)	57.8 (14.3)			.74*
Males	39 (62.9)	110 (61.1)	0.92	0.51-1.68	.92†
Smoking	17 (27.4)	17 (9.4)	3.62	1.71-7.66	**.001**†
Alcohol drinking	13 (20.9)	27 (15)	1.5	0.72-3.14	.37†
Coca chewing	39 (62.9)	58 (32.2)	3.57	1.95-6.52	**<.001**†
Poor oral condition	51 (81.1)	120 (67.7)	0.48	0.25-0.93	**.02**†
Denture wearing	24 (38.7)	81 (45)	0.6	0.3-1.02	.06†

Bold fonts indicate statistical significance.
OSCC, oral squamous cell carcinoma; OR, odds ratio; CI, confidence interval.
*According to *t* test.
†Crude odds ratios are informed, according to X^2.

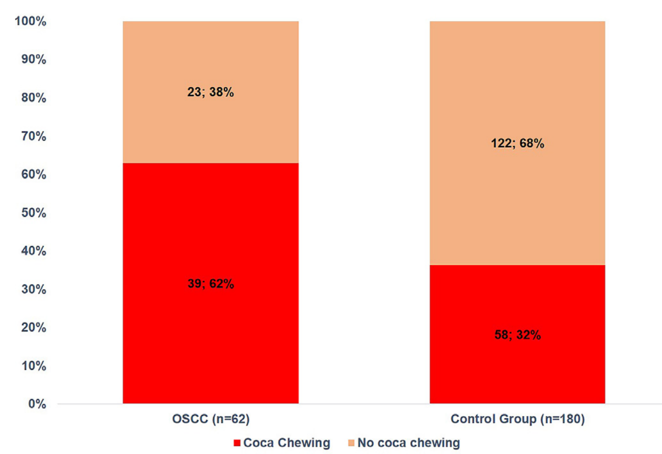

Fig. 3. Frequency of CC between both study groups (OSCC vs control group). $P < .001$ (X^2). OSCC, oral squamous cell carcinoma; CC, coca chewing.

studies, dating back to 1975, have demonstrated histopathological changes in the oral mucosa exposed to CC. Borghelli et al.[27] conducted a study in Humahuaca, Argentina, where biopsies were taken from the buccal mucosa of patients who chewed coca. They found that 65.2% of cases exhibited leukoedema and 21.3% showed leukoplakia. These lesions consistently coincided with the site where the coca leaf bolus was typically kept. Similarly, a Peruvian study conducted in 2005 described hyperkeratotic lesions associated with the mechanical and chemical irritation of CC (P = .010).[28] Notably, Nersesyan et al.[29] found no induction of nuclear anomalies reflecting genetic damage in buccal mucosa exfoliated cells from Peruvian coca chewers in the highest exposure group. However, they noted significantly elevated levels of karyorrhexis and karyolysis reflecting cytotoxic effects, which increased with daily consumption and with the addition of other components to improve the release of alkaloids. The authors indicated that unlike other chewing habits (betel, tobacco, and khat), CC does not induce genetic damage in oral keratinocytes. However, it's

Table III. Logistic regression analysis according to OSCC and control groups

Risk factor	*OSCC*	*Control*	*OR*	*LL CI 95%*	*UL CI 95%*	*P value*
Smoking	17/62	17/180	2.77	1.23	6.25	**.0139**
Poor oral condition	51/62	120/180	3.08	1.62	5.85	**.0006**
Coca Chewing	39/62	58/180	2.98	1.58	5.63	**.0007**

Bold fonts indicate statistical significance. There were included those variables that showed statistical significance in the bivariate analysis in Table II.
OSCC, oral squamous cell carcinoma; OR, odds ratio; LL, lower limit; UL, upper limit; CI, confidence interval.

Table IV. Risk factors—stratified analysis—according to coca chewing

	Chi-square		Multivariate logistic regression	
Risk factor	*Non-CC*	*CC*	*Non-CC*	*CC*
Tobacco	3 (0.8-10-3)	2.7 (1-7)	3 (0.7-12.4)	4.1 (1.2-13.1)
	P = .08	**P = .039**	P = .12	**P = .018**
Alcohol	1.5 (0.4-5.5)	0.9 (0.3-2.2)	1.08 (0.24-4.9)	0.26 (0.08-0.9)
	P = .54	P = .83	P = .9	**P = .035**
Poor oral health	2 (0.8-5.1)	4.4 (1.8-10.7)	2.1 (0.8-5.4)	6.6 (2.3-18.8)
	P = .12	**P = .0006**	P = .12	**P = .0003**

OSCC, oral squamous cell carcinoma; CC, coca chewing.

Table V. OSCC anatomic site according to coca chewing

Anatomic site	*OSCC with CC*	*OSCC without CC*	*OR (CI 95%)*	*P value (X^2)*
GBC	28 (72%)	8 (35%)		**.011**
Tongue	9 (23%)	10 (43%)		
Floor of mouth	2 (5%)	5 (22%)		
Total	39	23		
GBC vs other sites				
GBC	28 (72%)	8 (35%)	4.77 (1.58-14.4)	**.004**
Other sites	11 (28%)	15 (65%)		

OSCC, oral squamous cell carcinoma; CC, coca chewing; GBC, gingivobuccal complex; CI, confidence interval.

worth noting that this study only included healthy individuals without dental problems who were not taking any medication.

Due to the limited literature on this topic, there is no established cut-off point for recording the variable of accumulated exposure to CC. Espeza et al. defined coca chewers as those patients who engage in the habit 3 to 7 times per week.[30] However, given that CC is a traditional habit in our region, we considered an individual a habitual coca-chewer when they reported practising the CC habit for at least 6 hours per day. However, further studies are needed to validate these results. The challenge lies in identifying different degrees of severity of the habit to establish a risk stratification for coca chewers.

In the present study, classical risk factors for OSCC were investigated. Although tobacco showed statistically significant differences between both groups (both in the bivariate analysis and in the logistic regression, with P values of .001 and .0139, respectively), it was an uncommon habit in the overall group when compared to other similar studies from Latin America and Argentina.[8,31] Accordingly, in the 4th National Survey of Risk Factors conducted by the Ministry of Health of Argentina, the prevalence of smoking in the province of Salta between the years 2013 and 2018 ranged around 22%.[32] Additionally, only 16% of the included individuals were chronic drinkers, with no statistically significant differences observed. These findings suggest that there is a segment of the population not exposed to classical risk factors for OSCC, such as tobacco and alcohol, and yet still develop OSCC, indicating potential exposure to nonconventional risk factors.

In our study, the oral health status of the included patients resembled descriptions in Asian reports, where betel-chewing associated OSCC or its most frequent precancerous condition, oral submucous fibrosis, is typically associated with a clinical context of severe periodontal disease, multiple tooth loss, and sharp dental surfaces representing potential traumatic and chronic-inflammatory sources.[33,34] In our setting, the overall sample exhibited a prevalence of 70% of patients with poor oral health. Furthermore, the OSCC group demonstrated a high prevalence of this variable (81%). This suggests a potential interaction between CC and poor oral conditions. The results of the multivariate analyses, whether stratified or not according to CC suggest that tobacco and poor oral hygiene increase the risk of OSCC in patients who consume coca. However, in the absence of these 2 factors, CC could potentially act as an independent risk factor for OSCC in this population.

The biological pathways through which CC could potentially induce cellular damage and malignant transformation of oral keratinocytes remain largely unknown. Given the significant similarities between CC and the well-known habit of areca nut or betel chewing, it is plausible that some of the phenomena described in those patients may also be relevant to CC-

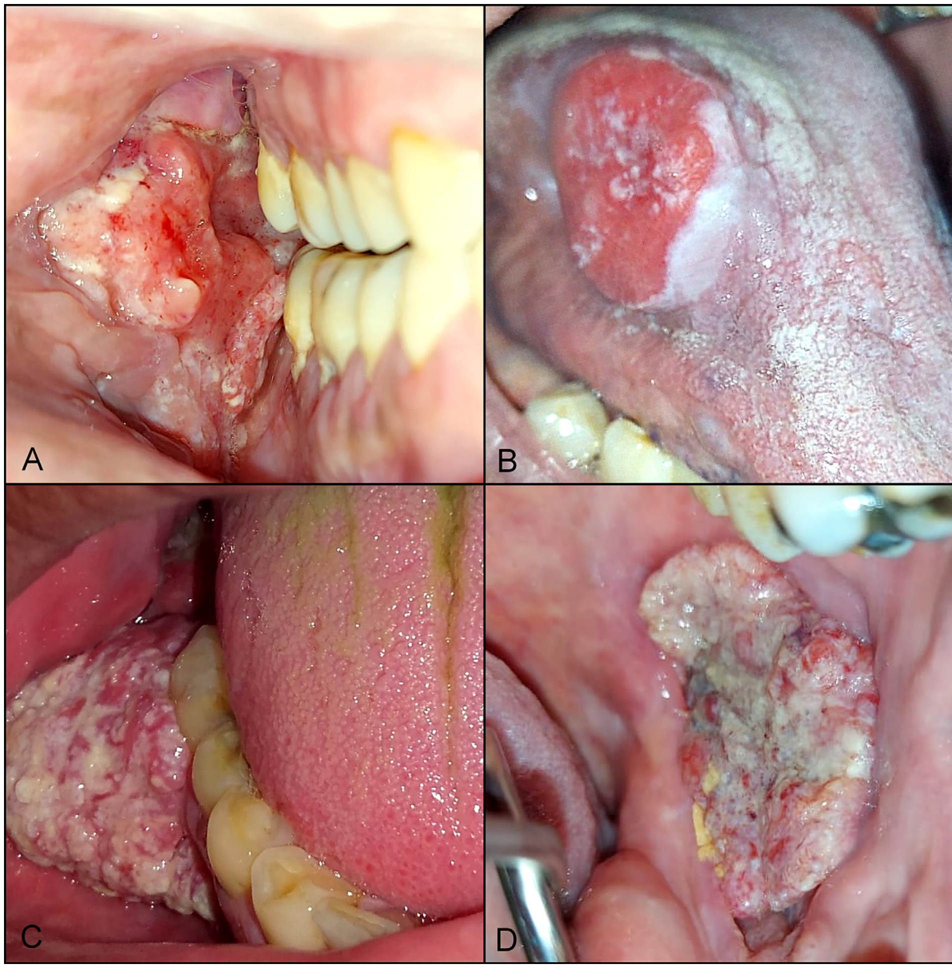

Fig. 4. CC-associated OSCC. A, C, and D depict classical cases of OSCC with involvement of the gingivobuccal complex. A, Male, 56 years old, presenting with a tumoral lesion in the right GBC. The patient had a CC habit for more than 10 hours a day, without classical risk habits for OSCC. B, Male, 66 years old, heavy smoker, with an ulcerated tumor on the right ventrolateral

associated carcinogenesis. Current evidence indicates that the areca nut induces multiple cytotoxic effects, including inflammation, tissue hypoxia, DNA damage, etc. These cellular effects are accompanied by several molecular alterations involving the production of reactive oxygen species, activation of signaling pathways, promotion of epithelial-mesenchymal transition, and facilitation of cancer stemness conversion.[35] To the best of our knowledge, the coca leaf itself does not possess carcinogenic or mutagenic potential.[29,36,37] However, the functional dynamics of CC could potentially lead to long-standing damage, ultimately promoting the onset of dysplastic and, subsequently, malignant phenomena. Additionally, the supplementary components added to the acullico during chewing may contribute to chronic damage. For example, sodium bicarbonate added to the bunch of coca fibers has been shown to induce periodontal lesions.[38,39] Nonetheless, the alkaloids contained in the unprocessed coca leaf are found at very low levels.[40]

CC is a habit intrinsically linked to constant irritation or chronic mechanical irritation (CMI) of the oral mucosa, particularly in the affected area where the coca leaf bolus (acullico) is commonly placed, often on the GBC. The roughness, irregularity, and hardness of the coca leaf fibers (which are exacerbated if tree ashes are added), along with mucosal movements and the direct impact of the edges of occlusal dental surfaces, may result in silent but chronic trauma. CC-associated OSCCs fulfill the criteria of CMI as postulated in epidemiological studies that address the relationship between chronic trauma and oral carcinogenesis.[41,42] Therefore, CMI could also serve as a promoter of oral carcinogenesis associated with CC, leading to chronic inflammation or a longstanding proliferation of immature oral keratinocytes through repetitive cycles of trauma, wound healing, and re-injury.[43] Additionally, CMI may facilitate the deeper penetration of other mutagenic products of tobacco and alcohol, or biological carcinogens such as periodontal infections and oncogenic human papillomavirus, into the epithelial layers.[44−46] Experimental studies have shown that a chronically damaged or traumatized mucosa is more permeable to the penetration of carcinogens.[47,48]

Our study revealed, for the first time, a high frequency of GBC-OSCC in Northern Argentina, surpassing even the lateral border of the tongue, which is the most common location for OSCC in South America (Figure 4).[8] Sozio et al.[49] reported that South Asians residing in the United States have a higher incidence of buccal mucosa/vestibule OSCC, suggesting that the aetiology behind this particular subsite of OSCC is linked to a social habit. Despite the differences in biological pathways, coca, and betel chewing habits share similarities in terms of anatomical location and clinical presentation regarding their potential role in oral carcinogenesis. These parallels lead us to hypothesize that OSCC associated with CC may share etiological mechanisms with the well-known Indian cancer.[50]

Our study presented some limitations for example the lack of accurate quantification of the volume of coca consumed, which could determine if a dose-response relationship exists.

Further studies should also explore additional etiological cofactors reported in various studies addressing OSCC associated with chewing habits, such as iron, zinc, copper, vitamin, or nutritional deficiencies, human papillomavirus infection, among others. Factors such as the size of the coca bunch, different subtypes of coca, mutagenic effects, or other ingredients such as lime or ashes, as well as the duration of the habit per day, should also be incorporated into future research protocols.

Additionally, a key limitation of this study is the lack of systematic recording of oral potentially malignant disorders (OPMD) prior to the development of CC-associated OSCC. The Kuala Lumpur Consensus (1996), and its subsequent publication addressing oral mucosal lesions associated with betel quid, areca nut, and chewing habits could serve as a useful guideline in determining variables for the analysis of CC and its precursor lesions of CC-associated OSCC. This workshop primarily discussed oral conditions demonstrated to be specifically associated with chewing habits.[51] Interestingly, in the control group of our study (although without having been systematically recorded), some clinical aspects of a *chewer's mucosa* described in the aforementioned consensus were evidenced (the tendency of the oral mucosa to desquamate, detached tags of tissue with a pseudomembranous appearance, and yellowish or greenish-brown encrustations from coca leaves). This is a critical issue since identifying a specific precursor lesion could facilitate the early diagnosis of OSCC in coca chewers. Further studies should investigate whether CC-associated OSCC could arise from a specific precursor lesion, a well-known OPMD (e.g., leukoplakia or erythroplakia) or *de novo*.

Finally, this study sheds light on a new perspective in the investigation of regional risk factors for OSCC specifically within Latin America. One of the reported barriers to the early diagnosis of OSCC in South America and the Caribbean includes weaknesses in oral cancer control strategies, low reporting for OPMD and OSCC, unclear referral pathways, and a lack of adequately trained professionals. Promoting opportunistic OSCC screening, developing oral cancer screening campaigns, implementing telemedicine for well-defined referral systems for patients with OPMD and OSCC in low-income areas such as Salta, and documenting specific risk factors such as CC could improve existing strategies for primary prevention of Oral Cancer.[52]

CONCLUSION

This study represents the first demonstration of a significant association between CC and OSCC in Northern Argentina. Further studies are warranted, considering that this particular habit, from a multifactorial perspective, may be classified as a noncanonical risk factor for oral cancer in South America. An understanding of the underlying biological mechanisms of this habit throughout the sequence of oral carcinogenesis would be instrumental in developing prevention and cessation campaigns for CC. Additionally, conducting additional studies in other geographic regions where coqueo is prevalent could offer further scientific evidence on the association between CC and OSCC.

DECLARATION OF INTERESTS

None.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Ignacio Molina-Ávila: Writing − original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Juan Martín Pimentel-Solá:** Writing − original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Emilio Buschiazzo:** Writing − original draft, Supervision, Resources, Investigation, Formal analysis. **Adriana Echazú:** Data curation, Formal analysis, Methodology, Supervision. **Eduardo Piemonte:** Writing − review & editing, Writing − original draft, Formal analysis, Investigation, Resources, Software, Supervision. **Gerardo Gilligan:** Writing − review & editing, Writing − original draft, Supervision, Methodology, Formal analysis, Conceptualization.

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