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ORIGINAL ARTICLE

Chronic mechanical irritation enhances the effect of tobacco and alcohol on the risk of oral squamous cell carcinoma: a case-control study in Argentina

Eduardo David Piemonte[1] · Jerónimo Pablo Lazos[1] · Gerardo Marcelo Gilligan[1] · René Luis Panico[1] · Laura Cecilia Werner[2] · Yi-Hsin Yang[3] · Saman Warnakulasuriya[4]

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Abstract

Objectives Oral squamous cell carcinoma (OSCC) is a multifactorial disease. The individual effect of each risk factor for OSCC may be conditioned by the frequency of other factors. The objective of this study was to identify the association between chronic mechanical irritation (CMI) and OSCC and to analyse the influence of CMI on other important risk factors for OSCC.

Materials and methods A prospective and age/sex-matched case-control study was performed in two institutions from Argentina between 2009 and 2019, with consecutive and newly diagnosed OSCC. The frequencies of tobacco, alcohol, and CMI were analysed using conditional logistic regression. Cumulative tobacco consumption and the presence of CMI were analysed using the Mann-Whitney test.

Results CMI and OSCC were associated with an *OR* of 7.02 (95% *CI* 3.57–13.78, $p < 0.001$). The combination of CMI and alcohol demonstrated the highest risk of OSCC (*OR* 53.83, *CI* 95% 8.04–360, $p < 0.0001$), followed by the combination of CMI, tobacco, and alcohol (*OR* 48.06, *CI* 95% 8.47–272, $p < 0.0001$). The combination of CMI and tobacco was also significant (*OR* 5.61, *CI* 95% 1.07–29.54, $p = 0.042$). Patients with CMI developed OSCC with less cumulative tobacco use compared with those without CMI.

Conclusion CMI is an independent risk factor for OSCC, and it could act as a risk modifier among tobacco and alcohol users having an enhancing effect.

Clinical relevance Elimination of CMI could decrease the risk of OSCC.

Keywords Tobacco · Alcohol · Chronic mechanical irritation · Oral squamous cell carcinoma · Risk factors · Case-control study

Introduction

The major risk factors associated with oral squamous cell carcinoma (OSCC) are well described in the literature, including consumption of tobacco (smoked or smokeless), excess consumption of alcohol, and use of betel quid (areca nut) [1]. Human papillomavirus (HPV) is an emerging risk factor [2]. Additional causative factors for oral cancer considered as controversial have been discussed, but there has been no agreement regarding those [3].

✉ Eduardo David Piemonte
eduardo.piemonte@unc.edu.ar; epiemonte@yahoo.com

Jerónimo Pablo Lazos
jerolazos@gmail.com

Gerardo Marcelo Gilligan
ggilligan@unc.edu.ar

René Luis Panico
renepanico@hotmail.com

Laura Cecilia Werner
laucwerner@gmail.com

Yi-Hsin Yang
yhyang@nhri.edu.tw

Saman Warnakulasuriya
saman.warne@kcl.ac.uk

1 Oral Medicine Department, Dentistry College, Universidad Nacional de Córdoba, Av. Haya de la Torre s/n, Ciudad Universitaria, 5000 Córdoba, Argentina

2 Oral Medicine Service, Hospital Alemán, Buenos Aires, Argentina

3 National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

4 Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London & WHO Collaborating Centre for Oral Cancer, London, UK

One of these controversies relates to chronic mechanical irritation (CMI), and this possible association was considered since the beginning of the twentieth century [4]. The harmful effects of CMI are generated by persistent, recurrent friction or pressure from dental or prosthetic factors on the oral mucosa, often facilitated by functional or parafunctional activities of the oral musculature or dental occlusion [5]. There is experimental evidence from in vivo animal models confirming that CMI exerts a promoting effect on carcinogenesis [6]. In recent reviews addressing the association of CMI with oral cancer, mostly, case reports or case series were included [7–10]. Using the Bradford-Hill criteria to analyse relationships, CMI could be considered a possible risk factor for OSCC, although scientific evidence is limited and inconclusive [11].

OSCC is multifactorial, as evidenced by the fact not all smokers and/or drinkers develop OSCC, whereas not all patients with OSCC have been smokers and/or drinkers [12]. Evidence suggests that tobacco and alcohol are not necessary nor sufficient causes since OSCC is multifactorial and the individual effect of each factor may be conditioned by the frequency of other factors [13]. The role of CMI and its interaction with other well-known risk factors in the causation of OSCC requires further study [14]. The promoter role of CMI could therefore act as a potentiator of the effect of tobacco and/or alcohol in oral carcinogenesis. Thus, the objective of this study was to identify the association between chronic mechanical irritation (CMI) and OSCC and to analyse the influence of CMI on other major risk factors for OSCC.

Material and methods

Study design

We conducted a prospective and age/sex, one-to-one matched case-control study between 2009 and 2019 at Dentistry College of the Universidad Nacional de Córdoba and the Oral Medicine Service of the Hospital Alemán of Buenos Aires (both in Argentina). The STROBE guidelines were used to ensure satisfactory reporting of this observational study.

Cases

Eligible cases were individuals ≥ 18 years with consecutive and newly diagnosed OSCC, seen in the Oral Medicine Departments of the two institutions. Anatomical locations included OSCC of lip mucosa and the oral cavity (ICD-10 C00, C02-06). Malignant tumours of major salivary glands and oropharynx, sarcomas, and lymphomas were excluded. An incisional biopsy was taken from all cases for histopathology confirmation. The exclusion criteria were those who had any previous treatment for head and neck cancer at the time of recruitment or did not consent to be included in the study.

Controls

Eligible controls were individuals ≥ 18 years seeking general dental treatment in the same institution as the case group they belonged to, without oral cancer or oral potentially malignant disorders (OPMD). The controls were included consecutively at the same time as the cases. All controls were frequency-matched to cases by sex and age (± 2 years). If there were several potential control subjects for the same OSCC case, the respective match was chosen at random.

Assessment of included variables

Cases and controls underwent identical interviews by calibrated investigators. For the clinical recording of CMI, agreement of two operators was required. A standardized questionnaire was used (available on request from the authors) with information regarding sociodemographic variables including detailed smoking and alcohol drinking histories. Data related to anatomical location and size of the OSCC were also recorded, and the latter was measured clinically.

All individuals were interviewed in detail regarding CMI, which was considered present on previously healthy mucosa or on pre-existing pathologies when any of the following criteria was found as defined by Piemonte et al. [15]:

- Clinical lesion compatible with a traumatic origin, of 1 month or more of evolution, with static contact, or by functional or parafunctional movements (dysfunctional swallowing, lingual interposition, unilateral chewing, sucking, nibbling, stabilization of prosthesis with the tongue or lips, among others) with any potentially traumatizing agent of dental or prosthetic origin, which must have existed before the injury or the aggravation of a pre-existing injury.
- History of chronic or recurrent mouth ulcer, for more than a month, at the site of subsequent appearance of the OSCC, concerning dental, prosthetic, and/or functional CMI factors.
- OSCC with static, functional, or parafunctional contact with any potentially injuring dental or prosthetic factor provided that the alleged factor had existed in the mouth before patient acknowledgment of the OSCC. This data was obtained by anamnesis and/or oral inspection.

To determine CMI, first, a clinically visible lesion was identified, also inquiring about its evolution time. The functional-topographic relationship was then explored, ascertaining defective dental or prosthetic elements in contact with the lesion. Once the injuring factor was acknowledged, its duration within the mouth was queried. Clinical inspection was used to ascertain presence of a lesion, the injuring factor, and the functional-topographic relationship between them. If a traumatic factor could not be found on examination, anamnesis was used to find out if a tooth or denture injured the lesion's area before its appearance. The evolution time of the lesion and the duration of the injuring factor were ascertained by anamnesis. If the factor had more time than the evolution time of the lesion, the temporality criterion was considered fulfilled. Figure 1 details the procedure to determine compliance with these CMI criteria.

Concerning tobacco use, patients were classified as *never smokers* or *smokers*. Never smokers were individuals who not smoked throughout their life. Smokers were defined as subjects who had smoked at least one cigarette/day from the previous year to present day. The different types of [smoked] tobacco were converted to cigarette equivalents (1 cigar = 4 cigarettes and 1 pipe = 3.5 cigarettes). Lifetime tobacco exposure was calculated as the product of daily frequency and duration of smoking, expressed in pack-years. For the statistical analysis, the combined distribution was dichotomized according to the median.

Alcohol exposure was classified as drinker or never or non-drinker. Drinkers were defined as those subjects who drank at least one drink unit weekly during the last year, and non-drinkers were classified as subjects who never consumed alcohol or had less than one drink per week.

Statistical analysis

The categorical variables were presented as frequencies and percentages; and mean and standard deviations were used for numerical variables. Since this study is a matched case-control design, the McNemar test was used for comparing categorical variables and Wilcoxon signed-rank test was used for comparing numerical variables between the OSCC and control group. The conditional logistic

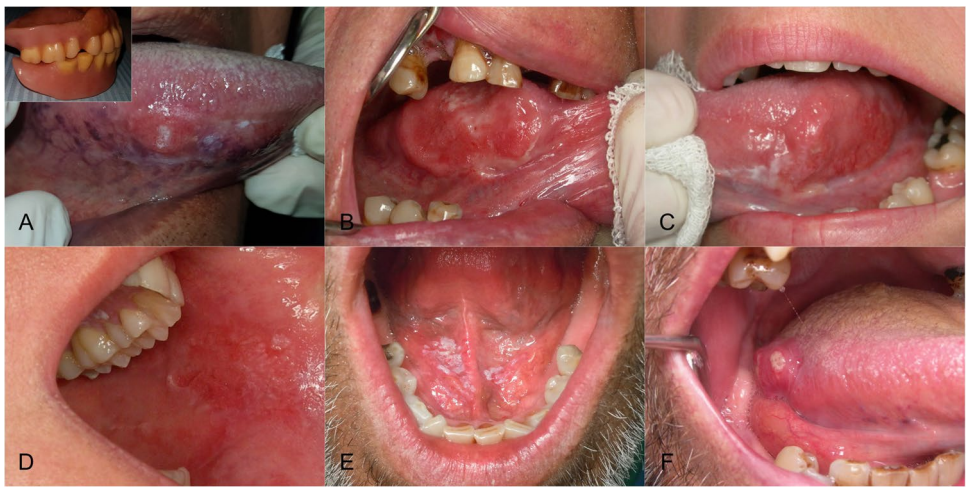

Fig. 1 OSCC cases with clinical criteria for chronic mechanical irritation (CMI) identification. **A** Male, 72 years. Past heavy smoker, never drinker. Tumour of 1.5 cm in diameter with 3 months of evolution, surrounded by whitish lesions. He used a complete denture over a 10-years-period, with loss of retention and stability. For more than 2 years, the patient stabilized the prosthesis with his tongue, interposing it in the occlusal area. CMI positive. Diagnosis: moderately differentiated-OSCC. **B** Male, 77 years, heavy smoker, heavy drinker. Ulcerated tumour of 4 months of evolution associated with upper and lower teeth. Diastemas and loss of several teeth allowed tongue interposition among those edentulous spaces for several years. CMI positive. Diagnosis: moderately differentiated-OSCC. **C** Female, 41 years, non-smoker, light drinker. Ulcerated tumour of 6 months of evolution, in relation to lingualized lower left molars. Narrow dental arches, early loss of the first lower molar, and left unilateral chewing pattern facilitated lingual interposition and increased the intensity and frequency of traumatic contact, at least since the loss of the lower-left molar (more than 8 years) CMI positive. Diagnosis: well-differentiated OSCC. **D** Female, 31 years, light smoker, light drinker, HPV 16 by PCR. Erythroplastic lesion of 1 year of evolution, related to sharp upper left bicuspids, in an individual with the habit of cheek biting for several years. Whitish leukoplastic lesions, not associated with traumatic factors, were evidenced in other areas of the mucosa, fulfilling criteria for proliferative verrucous leukoplakia. CMI positive. Diagnosis: microinvasive-OSCC. **E** Male, 56 years, heavy smoker, heavy drinker. A verrucous lesion with foci of red areas on the floor of the mouth, with at least 3 years of evolution. No tooth or prosthesis was identified in contact with the lesion. CMI negative. Diagnosis: poorly differentiated-OSCC. **F** Male 65 years, heavy smoker and heavy drinker. Tumour of 2 cm in diameter with 2 months of evolution. On clinical examination, no teeth or dentures were in contact with the tumour. The patient revealed having a tooth extraction next to the tumour area, a year ago, but he denied a history of dental trauma. CMI negative. Diagnosis: well-differentiated OSCC

regression was adapted to compute odds ratios (OR) and 95% confidence intervals. Since the cell sizes were sparse, age was stratified into 3-year intervals in the conditional logistic regression.

As a complementary analysis, among smokers, the difference in cumulative consumption in pack-years according to OSCC and CMI status was compared using the Mann-Whitney test.

Ethical approval

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Council of Ethical Evaluation of Health Research under the Ministry of Health of the Province of Córdoba (N° 1378), by the Institutional Committee of Ethics in Health Research of the Faculty of Dentistry of the University of Córdoba (11T/2016), and by the Research Ethics Committee of the Hospital Alemán, Buenos Aires, Argentina (registration code 3674). All cases and selected controls who agreed to participate in the study signed an informed consent.

Results

Clinical and demographic characteristics

The study included 106 consecutive cases and 106 controls matched by age and gender, 21 were from Buenos Aires and 85 from Cordoba; 61 (57.5%) were male, while 45 (42.5%) were female, with a male:female ratio of 1.35:1 (Table 1).

The age showed a mean of 63.78 years for the OSCC group and 63.74 years for the control group (Table 1). Women were older than men; in the oral cancer group, the mean age of men was 60.8 years versus 67.8 years for women (Wilcoxon test, $p = 0.01$).

In the OSCC group, the tongue was the most common site, with more than 57% (61/106), followed by gum and buccal mucosa (9/106 each). According to the TNM classification, T1 and T2 represented 70% of OSCC cases.

Univariate analyses

Tobacco consumption was reported by 44.3% of the OSCC group and in 48.1% of the control group. Tobacco use categorized as YES/NO did not show statistically significant differences between the OSCC and control. Although cumulative tobacco consumption was higher in the OSCC group, it did not present a statistically significant difference compared with control. When tobacco consumption was categorized according to cumulative consumption levels, higher tobacco consumption was associated with the OSCC group, whereas lower tobacco consumption with the control, and never smokers had a similar distribution in both groups. Heavy tobacco use was associated with a higher risk of OSCC ($p = 0.047$) when pairing together never smokers and light smokers in one category (Table 1).

Alcohol consumption categorized as YES/NO was statistically associated with a higher risk of oral cancer, with 50% of patients who reported drinking alcohol in the OSCC group vs. 34% in the control group ($p = 0.007$).

In the OSCC group, 73.6% ($n = 78$) showed evidence of CMI while in the control group 32.1% ($n = 34$) had CMI, with a statistically significant association with increased risk of OSCC ($p < 0.001$) (Table 1). Chronic trauma from removable ill-fitting dentures was the most common cause for CMI — close to a third — in the OSCC group. The combination of a fixed traumatic factor and a functional factor was the second most frequent CMI condition, with just over a quarter in the OSCC group (Table 2).

Conditional logistic regression

The conditional logistic regression analysis based on the age and gender matched data has provided a controlling of possible confounding variables. The univariate conditional logistic regression showed CMI with an *OR* of 7.02 (95% *CI* 3.57–13.78, $p < 0.001$), and alcohol consumption had an *OR* of 2.20 (95% *CI* 1.22–3.98, $p = 0.009$). Tobacco categorized as YES/NO exhibited an *OR* of 0.76 (95% *CI* 0.40–1.46, $p = 0.413$), while when categorized in two groups according to cumulative consumption displayed a higher risk of OSCC, with an *OR* of 2.24 (95% *CI* 1.11–4.55, $p = 0.025$) (Table 3).

The multivariable analysis on the CMI, tobacco, and alcohol was modelled as combinations of the three habits. The interaction between the recorded variables is shown on Table 4. The absence of the three factors was more frequent in the control group (23.6% vs. 5.7%). Meanwhile, finding those three factors simultaneously was more frequent in the OSCC group, with statistically significant differences (20.8% vs. 4.7%, $p = 0.016$).

The occurrence of each factor individually was more common in the OSCC group for CMI (32.1% vs. 10.4%, $p = 0.017$). Independently, tobacco and alcohol consumption were more frequent in the control group, although with no statistical difference.

When the different combinations of the studied factors are considered, all of them displayed a higher risk for OSCC. The combination of CMI and alcohol demonstrated the highest risk of OSCC (*OR* 53.83, *CI* 95%

Table 1 Clinical and demographic characteristics of cases and controls of the study

	OSCC group		Control		*p*-value*
	n	%	*n*	%	
Total	106		106		
Gender					
Male	61	57.5%	61	57.5%	
Female	45	42.5%	45	42.5%	
Age (in years)					
Mean (sd)	63.78	(14.51)	63.74	(14.51)	
Tobacco					
Yes	47	44.3%	51	48.1%	0.586
No	59	55.7%	55	51.9%	
Cumulative tobacco consumption# (in pack-year)					
Mean (sd)	14.79	(26.38)	8.4	(12.52)	0.839
Frequency of tobacco consumption[†]					
No	59	55.7%	54	50.9%	**0.031**
Light: less than or equal to median	16	15.1%	34	32.1%	
Heavy: more than median	31	29.2%	18	17.0%	
Categories of tobacco consumption					
No smokers & light smokers	75	70.8%	88	83.0%	**0.047**
Heavy smokers	31	29.2%	18	17.0%	
Alcohol					
Yes	54	50.9%	36	34.0%	**0.007**
No	52	49.1%	70	66.0%	
Chronic mechanical irritation					
Yes	78	73.6%	34	32.1%	**< 0.001**
No	28	26.4%	72	67.9%	

*According to McNemar test; *sd*, standard deviation; [†]categorized according to the median of smokers' tobacco consumption, equal to 16.8 pack-years; #, due to heavy skewness of distribution, statistical testing was conducted at the natural logarithm of pack-year [log (pack-year + 1)] using the Wilcoxon signed-rank test. Bold fonts indicates statistical significance

Table 2 Factors causing chronic mechanical irritation in the OSSC group

Type of factor	*n*	%
Fixed appliance	12	15.3%
Removable appliance	24	30.6%
Functional cause	4	5.2%
Fixed + functional	21	26.9%
Removable + functional	9	11.6%
Fixed + removable	4	5.2%
Fixed + removable + functional	4	5.2%
Total	78	100%

Fixed or dental factors: teeth, implants, restorations, or fixed prostheses with sharp or broken surfaces, and/or invading functional spaces of the oral mucosa. Removable or prosthetic factors: removable dentures with rough or sharp surfaces, over-extended flanks, unsupported retainers, or invading functional spaces of the oral mucosa, ill-fitting dentures. Functional factors: dysfunctional swallowing, tongue interposition, unilateral chewing, sucking, nibbling, stabilization of dentures with the tongue or lips

8.04–360, $p < 0.0001$), followed by the combination of CMI, tobacco, and alcohol (*OR* 48.06, *CI* 95% 8.47–272, $p < 0.0001$). Those combinations presented an additive or synergic interaction. The combination of CMI and tobacco produced a sub-additive or antagonistic interaction (*OR* 5.61, *CI* 95% 1.07–29.54, $p = 0.042$). But homogeneously, CMI acted as a positive modifier of the effect of tobacco and/or alcohol.

Complementary analysis

Among smokers, the patients with OSCC without CMI had cumulative tobacco consumption (49 pack-years) higher than patients with OSCC and CMI, and controls with or without CMI (24.4, 13.6, and 19.2 pack-years, respectively), with significant differences. Meanwhile, the patients in the control group and the patients with OSCC with CMI did not show significant differences (Table 5).

Table 3 Odds ratios from univariate conditional logistic regression

	OSCC		Control		*OR*	95% *CI*		*p*-value
	N	%	*N*	%		LL	UL	
Tobacco								
Yes	47	44.3%	52	49.1%	0.76	0.40	1.46	0.413
No	59	55.7%	54	50.9%	ref			
Frequency of tobacco consumption[†]								
No	59	55.7%	54	50.9%	ref			
Light: less than or equal to median	16	15.1%	34	32.1%	0.38	0.17	0.85	**0.018**
Heavy: more than median	31	29.2%	18	17.0%	1.50	0.69	3.27	0.311
Categories of tobacco consumptiom								
No smokers & light smokers	75	70.8%	88	83.0%	ref			
Heavy smokers	31	29.2%	18	17.0%	2.24	1.11	4.55	**0.025**
Alcohol								
Yes	54	50.9%	36	34.0%	2.20	1.22	3.98	**0.009**
No	52	49.1%	70	66.0%	ref			
Chronic mechanical irritation								
Yes	78	73.6%	34	32.1%	7.02	3.57	13.78	**< 0.001**
No	28	26.4%	72	67.9%	ref			

OSCC, oral squamous cell carcinoma; *OR*, odds ratio; *LL*, lower limit; *UL*, upper limit; *ref*, reference category; [†]categorized according to the median of tobacco consumption, equal to 16.8 pack-years. Bold fonts indicates statistical significance

Table 4 Conditional logistic regression according to combination of CMI, tobacco, and alcohol

CMI	Tobacco	Alcohol	OSCC		Control		*OR*	95% *CI*		*p*-value
			n	%	*n*	%		LL	UL	
No	No	No	6	5.7%	25	23.6%	ref			
Yes	No	No	34	32.1%	11	10.4%	29.75	6.25	141.50	**< 0.001**
No	Yes	No	5	4.7%	22	20.8%	2.01	0.43	9.47	0.378
No	No	Yes	4	3.8%	12	11.3%	3.02	0.49	18.52	0.233
Yes	Yes	No	7	6.6%	12	11.3%	5.61	1.07	29.54	**0.042**
Yes	No	Yes	15	14.2%	6	5.7%	53.83	8.04	360.38	**< 0.001**
No	Yes	Yes	13	12.3%	13	12.3%	10.68	2.13	53.54	**0.004**
Yes	Yes	Yes	22	20.8%	5	4.7%	48.06	8.47	272.58	**< 0.001**

CMI, chronic mechanical irritation; *OSCC*, oral squamous cell carcinoma; *OR*, odds ratio; *LL*, lower limit; *UL*, upper limit; *ref*, reference category. Bold fonts indicates statistical significance

Table 5 Lifetime tobacco exposure in smokers according CMI and OSCC

	CMI yes		CMI no		
	n	Pack years	*n*	Pack years	
Control	17	13.6	35	19.2	0.38*
OSCC	29	24.4	18	49	**0.0058***
		0.17*		**0.0001***	

CMI, chronic mechanical irritation; *OSCC*, oral squamous cell carcinoma; **p*-value according Mann-Whitney test. Bold fonts indicates statistical significance

Discussion

The causal association between CMI and OSCC has been proposed in the early twentieth century by Martin et al. [4]. However, human studies analysing the association between CMI and OSCC having statistical analysis are limited in the scientific literature (Table 6). There are 4 systematic reviews and/or meta-analyses, and three of them found a statistically significant association between CMI and OSCC. The more recent one used stringent inclusion criteria, including only one study with a high risk of bias according to the authors [10]. The review described features needed for proper observational studies on the topic. One of the most relevant aspects is the need to

Table 6 Available studies assessing the statistical association between CMI and OSCC

Author (year)	Study type	CMI description	Association CMI-OSCC
Velly (1998) [16]	Case-control	Oral sore secondary to ill-fitting dentures	*OR* 2.3 (95% *CI* 1.2–4.6)
		Broken teeth	*OR* 1.13 (95% *CI* 0.75–1.69)
Lockhart (1998) [17]	Case-control	Dental and prosthetic factors	No significant differences
Rosenquist (2005) [18]	Case-control	> 5 defective teeth	*OR* 3.1 (95% *CI* 1.2–8.2)
		Poorly fitting or defective complete dentures	*OR* 3.8 (95% *CI* 1.3–11.4)
Vaccareza (2010) [19]	Case-control	Recurrent sores by ill-fitting denture	*OR* 4.58 (95% *CI* 1.52–13.76)
Piemonte (2010) [5]	Cross-sectional	Chronic mechanical irritation	$p < 0.0001$
Bektas-Kayhan (2014) [20]	Case-control	Chronic trauma	$p = 0.0001$
Manoharan (2014) [7]	Meta-analysis	Denture	*OR* 1.42 (95% *CI* 1.01–1.99)
		Ill-fitting denture	*OR* 3.90 (95% *CI* 2.48–6.13)
Huang (2015) [21]	Case-control	Bad prosthesis	*OR* 2.33 (95% *CI* 1.79–3.04)
		Recurrent oral ulcerations	*OR* 3.96 (95% *CI* 2.11–7.44)
		Recurrent oral ulcerations in non-smokers	*OR* 5.21 (95% *CI* 2.42–11.18)
		Recurrent oral ulcerations in non-drinkers	*OR* 4.71 (95% *CI* 2.37–9.36)
Li (2015) [22]	Case-control	Repetitive dental ulcers	*OR* 5.12 (95% *CI* 3.17–8.28)
Singhvi (2017) [8]	Meta-analysis	Denture	*OR* 1.45 (95% *CI* 1.28–1.64)
		Ill-fitting denture	*OR* 2.62 (95% *CI* 2.1–3.25)
Piemonte (2018) [15]	Case-control	Chronic mechanical irritation	*OR* 4.84 (95% *CI* 2.12–11.08)
Chen (2018) [23]	Case-control	Repetitive dental ulcer (females)	*OR* 6.00 (95% *CI* 3.67–9.80)
		Repetitive dental ulcer (males)	*OR* 4.76 (95% *CI* 2.75–8.21)
Gupta (2021) [9]	Meta-analysis	Chronic mechanical irritation	*OR* 2.56 (95% *CI* 1.96–3.35)
Pentenero (2021) [10]	Systematic review	Chronic mechanical trauma/irritation	Not possible

CMI, chronic mechanical irritation; *OSCC*, oral squamous cell carcinoma

clearly define CMI as proposed by Piemonte et al. [15]. The *case group* should have OSCC diagnosed through histopathological examination, and the control group is to be devoid of malignancy. Also, patient recruitment should be done consecutively and synchronously and match cases and controls according to age and sex. They also note that the recording of the variables should be done in detail and prospectively, state exposition time and outcome in a standardized fashion, and the importance of controlling confounding factors. The present work indeed has all the requisites. Since prospective cohort studies for CMI and OSCC *are not feasible* for ethical reasons, our research approach may embody a high level of original epidemiological evidence on the topic.

Among the research dealing with CMI and OSCC, two studies found no statistically significant association [16, 17]. Those two studies had used a control group made up of other squamous cell carcinomas of the larynx and pharynx, while in the rest, the control group was hospital patients without cancer or patients requesting general dental care. Given that carcinomas of the larynx and pharynx share some causal factors with OSCC [24], using them in the control group could produce bias explaining the absence of any statistical association. Although the methods used to record CMI were somewhat heterogeneous, studies with carefully conformed control groups found a significant statistical association with OSCC, with an *OR* ranging from 2.3 to 6 [5, 15, 18–23].

In this context, our study showed that CMI is significantly associated with OSCC (*OR* 7.02, *CI* 95% 3.57–13.78, $p < 0.001$). Our data also exhibited that a higher risk of OSCC correlates with the interaction not only between tobacco and alcohol but also between those two factors and CMI. In our study, the combination of CMI with tobacco or alcohol showed a higher risk of OSCC (*OR* 5.61 and 53.83, respectively) when compared to tobacco or alcohol (*OR* 2.01 and 3.02). Confirming reported data from previous studies, CMI showed a statistical risk as an independent risk factor [15, 23].

It was interesting to note that, CMI also performed as a risk factor even in the absence of tobacco and alcohol (*OR* 29.75, *CI* 95% 6.25–141.50, $p < 0.001$). This does not mean that CMI is carcinogenic on its own, since so far its promoting effect has only been addressed in animal studies [6]. But unlike laboratory studies, humans are exposed to several carcinogenic factors, some still not identified. Thus, CMI could have a role in a multifactorial model even in the absence of tobacco and alcohol. An example of this could be the possible interaction between CMI and HPV, in which CMI could act as a

facilitator of HPV infection [25]. Some periopathogens have been reported with associations in oral cancer, likely acting similarly as CMI [26].

Unlike CMI, tobacco, and alcohol individually were not associated with a higher risk of OSCC in the factor interaction model, although in the logistic regression, they showed a statistically significant association. Tobacco and alcohol consumption are risk factors strongly associated with OSCC. However, the consumption levels differ substantially between countries, and even different consumption levels did not correlate consistently with a higher incidence of OSCC. For instance, in Latin America, Argentina reported approximately 30% of smokers against more than 50% in Chile, but the age-adjusted incidence rate of OSCC in Argentina is almost double than of Chile [27, 28]. Since there is no direct correlation in our study between tobacco consumption and OSCC occurrence, such discrepancies suggest other factors are also contributing.

Possibly the most important and original result of our work was when stratifying tobacco and alcohol risk according to CMI. It worked as an effect modifier in all categories of tobacco and alcohol consumption, increasing OSCC probability homogeneously. Conversely, the statistical interaction with alcohol and tobacco was heterogeneous. While for alcohol, CMI interacted synergistically with tobacco was antagonistic. This does not mean that tobacco and CMI are biologically antagonistic, but rather that their effects may be complementary.

In a multifactorial and multistage carcinogenesis model, the genetic damage produced by carcinogens such as tobacco and alcohol interact with non-genotoxic effects produced by chronic inflammation [29]. In this context, tobacco and alcohol may be responsible for the initiation of oral carcinogenesis, and CMI could act offering a promoting effect. Similar conditions arise when analysing the malignant transformation of OPMD, in which the causal factors of said malignancy are not necessarily the same as the OPMD [30, 31]. Those findings further support the need to study other less common risk factors and their interactions with tobacco and alcohol, which has been the objective of this work.

Our complementary results explain in part why tobacco and CMI present an antagonistic interaction. Smokers with OSCC presented a difference in cumulative tobacco consumption in association with CMI. Smokers without CMI developed OSCC after consuming two to three times more lifetime tobacco use than smokers with CMI or control patients. Additionally, smokers with CMI developed OSCC with marginally higher tobacco consumption than controls, although without statistically significant difference.

Based on these results, it appears that CMI complements the effects of tobacco. Thus, the effect of CMI could act modifying the damage of tobacco and/or alcohol, with an enhancing effect. This enhancing effect of CMI in OSCC could explain why in some individual oral cancer develops at a younger age, with less exposure to other carcinogens, or even has more aggressive behaviour. Although CMI might not be an initiator for OSCC, it is still a component cause in the multi-causal process for OSCC. Furthermore, CMI produced a high risk for an individual despite having smoked amounts of tobacco similar to the control group. The control and/or elimination of sources of CMI could hence reduce the incidence rates of OSCC. In this context, the detection, registration, and elimination of CMI by the dentist could play a role in oral cancer prevention.

Several dental variables have been proposed as risk factors for OSCC: periodontal disease having the most consistent results, also oral microbes, and CMI [26, 32]. All three have in common that they produce inflammation of the oral mucosa, and consequently, they can render promotion, having the capacity to alter the effects of carcinogens like tobacco and alcohol. However, most studies addressing risk or causative factors for oral cancer generally do not show the results adjusted by dental variables in the statistical analysis. As a result, there are no many studies to compare with the present work.

It is important to highlight that in our work, 70% of the OSCC were clinically classified as T1 and T2, which is a higher percentage of small (early) cancers than in most reports. This is likely because our research was carried out in institutions specialized in oral pathology and medicine, which have been participating in an oral cancer prevention program for several years. Said program was based on the training of dental students and health professionals, allowing the creation of a virtual network for diagnostic guidance and referral of early suspected cases to specialized clinics [33]. Most of the sample being T1 and T2 likely has a significant impact on the ability to properly record CMI. In malignancies larger than 4 cm (T3 and T4), it is difficult to ascertain whether CMI is a consequence of tumour growth invading dental or prosthetic spaces. In smaller OSCC, it appears to be easier to assess CMI, which should be done systematically through oral inspection and anamnesis.

Limitations

There are some study limitations in our study that require mentioning. Although the operators were calibrated for the detection of CMI and the kappa test showed very good interobserver agreement, this test was performed in only 40 patients, not in the whole sample. The distribution of the studied factors could vary in different populations, so our results cannot be generalized, needing to be validated in other geographical settings. Also, it is worth noting that the population under study had lower exposure to tobacco than other Latin American populations.

The risk of oral cancer produced by tobacco and alcohol can be established with greater precision when they are categorized according to the different levels of accumulated consumption [12]. The latter was only considered for tobacco in our study, but not for alcohol. The period of exposure to CMI was not investigated in our study. Our questionnaire did not include any information on mate drinking which could be an additional risk factor in this population.

Conclusions

CMI behaves as an independent risk factor, even in the absence of tobacco and alcohol consumption in this population. The promoting effect of CMI could exert a modifying effect on the damage generated by tobacco and/or alcohol, increasing the damaging effect. Our findings support the need to study less-known risk factors and their interactions with tobacco and alcohol.

Author contribution Conceptualization: EDP and SW. Methodology: EDP and SW. Formal analysis and investigation: EDP, JPL, GMG, RLP, LCW, Y-HY, and SW. Writing — original draft preparation: EDP, JPL, GMG, and SW. Writing — review and editing: EDP, JPL, GMG, RLP, LCW, Y-HY, and SW. Funding acquisition: EDP and GMG. Resources: EDP, JPL, and GMG. Supervision: SW.

Declarations

Ethics approval This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Council of Ethical Evaluation of Health Research under the Ministry of Health of the Province of Córdoba (N° 1378), by the Institutional Committee of Ethics in Health Research of the Faculty of Dentistry of the University of Córdoba (11T/2016), and by the Research Ethics Committee of the Hospital Alemán, Buenos Aires, Argentina (registration code 3674).

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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