LENI VERÔNICA DE OLIVEIRA SILVA

QUEILITE ACTÍNICA E CARCINOMA DE CÉLULAS ESCAMOSAS DE LÁBIO: *UM ESTUDO MULTICÊNTRICO*

Faculdade de Odontologia
Universidade Federal de Minas Gerais
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Leni Verônica de Oliveira Silva

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Orientador: Prof. Ricardo Alves de Mesquita

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“Os que se encantam com a prática sem a ciência são como os timoneiros que entram no navio sem timão nem bússola, nunca tendo certeza do seu destino.”

Leonardo Da Vinci

RESUMO

Este estudo investigou a frequência da queilite actínica (QA) e do carcinoma de células escamosas de lábio (CCEL) em diferentes regiões geográficas do Brasil realizando uma análise temporal dos casos por década. Também se estabeleceu o perfil dos pacientes e analisou os aspectos clínicos e histopatológicos. Em uma análise retrospectiva (1953-2018), arquivos de biópsias de 10 centros de Patologia Oral e Maxilofacial localizados em diferentes estados do Brasil: Pará, Rio Grande do Norte, Paraíba, Pernambuco, Rio Grande do Sul, Minas Gerais, Rio de Janeiro, São Paulo e Goiás foram analisados. O perfil da amostra, características clínicas e histopatológicas foram avaliados descritivamente e estatisticamente através dos testes qui-quadrado, ANOVA e t-Student utilizando o programa SPSS versão 23.0. Os laudos histopatológicos de QA e CCEL foram examinados de acordo com a classificação da Organização Mundial de Saúde (OMS) (2017). As análises estatísticas foram feitas utilizando o programa Dos 198.709 espécimes de biópsias, 2.017 casos de QA e 850 casos de CCEL foram avaliados, representando 1,0 e 0,4% das lesões orais, respectivamente. Em geral, indivíduos do sexo masculino (*n*QA=1.439, 71,4%; *n*CCEL=673, 79,3%), brancos (*n*QA=1.640, 87,3%; *n*CCEL=726, 91,3%), na sétima década de vida (*n*QA=570, 29,8%; *n*CCEL=222, 27,4%) com acometimento do lábio inferior (*n*QA=1.990, 98,7%; *n*CCEL=827, 97,3%) foram os mais afetados. Indivíduos fumantes e consumidores de álcool tiveram um maior grau de invasão nos casos de CCEL (*p*=0,004 e *p*=0,020) bem como indivíduos com história prévia de QA (*p*=0,018). A QA e o CCEL em estágios iniciais ainda são lesões subnotificadas no Brasil e negligenciadas por parte da população acometida. Novos dados sobre as características sociodemográficas e clinicopatológicas de 2.017 casos de QA e 850 casos de CCEL foram adicionados à literatura. Essa caracterização em um país tão grande e com tantas diferenças regionais como o Brasil fortalece evidências para clínicos, dermatologistas, estomatologistas e oncologistas e para o desenvolvimento de políticas públicas na prevenção dessas lesões na população brasileira.

Palavras-chave: Queilite. Neoplasmas. Carcinoma de células escamosas. Radiação solar. Medicina bucal. Patologia bucal. Epidemiologia.

ABSTRACT

Actinic cheilitis and Lip squamous cell carcinoma: multicenter study

This study investigated the frequency of actinic cheilitis (AC) and lip squamous cell carcinoma (LSCC) in different geographic regions of Brazil, making a temporal analysis of the cases per decade. It also established the profile of the patients with this lesion and analyzed the clinical and histopathological aspects. In a retrospective analysis (1953-2018), biopsy files of 10 Oral and Maxillofacial Pathology centers located in different states of Brazil: Pará, Rio Grande do Norte, Paraíba, Pernambuco, Rio Grande do Sul, Minas Gerais, Rio de Janeiro , São Paulo and Goiás were analyzed. The sample profile, clinical and histopathological characteristics were descriptively and statistically evaluated by chi-square, ANOVA and t-Student tests using the SPSS program version 23.0. Histopathological data of AC and LSCC were examined according to the World Health Organization (WHO) classification (2017). Of 198,709 specimens of biopsies analyzed, 2,017 cases of AC and 850 cases of LSCC were surveyed, representing 1.0 and 0.4% of the oral lesions, respectively. Overall, male patients (*n*AC=1,439, 71.4%; *n*LSCC=673, 79.3%), white (*n*AC=1,640, 87.3%; *n*LSCC=726, 91.3%), in their seventh decade of life (*n*AC = 570, 29.8%, *n*LSCC = 222, 27.4%) with involvement of the lower lip (*n*AC = 1.990, 98.7%, *n*LSCC = 827, 97.3%) were the most affected. Individuals smokers and alcohol users had a higher invasion grade in cases of LSCC (p=0.004 and p=0.020) as well as individuals with previous history of AC (p=0.018). The AC and the LSCC in early stage are still very underreported lesions in Brazil and neglected by the affected population. Novel data on the sociodemographic and clinicopathological features of 2,017 cases of AC and 850 cases of LSCC have been added to the literature. This characterization in such a large country and with so many regional differences as Brazil strengthens evidence for clinicians, dermatologists, stomatologists and oncologists and for the development of public policies for the prevention of these lesions in the Brazilian population.

Keywords: Cheilitis. Neoplasms. Carcinoma squamous cell. Solar radiation. Oral medicine. Pathology oral. Epidemiology.

LISTA DE ABREVIATURAS E SIGLAS

DPM	Desordem Potencialmente Maligna
QA	Queilite Actínica
UV	Ultravioleta
CCEL	Carcinoma de Células Escamosas de Lábio
OMS	Organização Mundial de Saúde
SPSS	Statistical Package for the Social Sciences

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1 CONSIDERAÇÕES INICIAIS

Queilite actínica (QA) é uma desordem potencialmente maligna (DPM) causada pela exposição crônica à luz solar ou radiação ultravioleta (UV) artificial (MARTINS-FILHO, DA SILVA, PIVA, 2011) que afeta mais comumente a região de vermelhão do lábio inferior de indivíduos do sexo masculino, na quinta década de vida e com pele clara (MARKOPOULOS, ALBANIDOU-FARMAKI, KAYAVIS, 2004; RODRÍGUEZ-BLANCO et al., 2018; WARNAKULASURIYA, JOHNSON, VAN DER WAAL, 2007). É caracterizada clinicamente por ressecamento, fissuras, áreas leucoplásicas, áreas atróficas, edema, eritema, úlcera e perda do limite do vermelhão do lábio (CAVALCANTE et al., 2008; JUNQUEIRA et al., 2011; ROSSOE et al., 2011).

Histologicamente, pode-se observar alterações do epitélio de revestimento pavimentoso estratificado que variam desde hiperqueratose e acantose a diversos graus de displasia epitelial. O tecido conjuntivo subjacente pode apresentar infiltrado inflamatório em região perivascular e comumente exibe degeneração basofílica do colágeno (DE SANTANA SARMENTO et al., 2014). Existem vários sistemas de classificação dos graus de displasia epitelial, todos objetivando chegar a um diagnóstico mais preciso das DPMs estabelecendo em que estágio de progressão a lesão se apresenta e determinando, por meio dos achados morfológicos e arquitetura tecidual, o prognóstico da lesão e o tratamento mais indicado (KUJAN et al., 2006; KUJAN et al., 2007; WARNAKULASURIYA, 2001). Dentre os sistemas de classificação, o da Organização Mundial de Saúde (OMS) é o mais amplamente utilizado e classifica a displasia em leve, moderada e severa a partir do somatório de alterações arquiteturais e citológicas (EL-NAGAR et al., 2017). Na displasia epitelial leve, as alterações arquiteturais e atipias celulares limitam-se ao terço inferior do epitélio; na displasia moderada, essas alterações se estendem pelos dois terços inferiores do epitélio; e, na displasia severa, são notadas alterações em mais de dois terços do epitélio. Entretanto, se ocorrem muitas atipias celulares, considera-se que a displasia é severa mesmo não atingindo mais que os dois terços inferiores do epitélio (EL-NAGAR et al., 2017).

Embora as estruturas da boca sejam facilmente acessíveis e lesões iniciais possam sinalizar o desenvolvimento dessa desordem, observa-se ainda que, em

muitos casos, há um atraso no diagnóstico (FERREIRA et al., 2016), sendo relatado uma taxa de transformação maligna que varia de 10% a 20% (MARKOPOULOS, ALBANIDOU-FARMAKI, KAYAVIS, 2004; SILVEIRA et al., 2009). Entretanto, esta taxa é difícil de se estimar fielmente, pois o limite entre lesões que realmente são QA ou que já se tratam de um carcinoma de células escamosas é bastante sutil (DANCYGER et al., 2018; DE ROSA et al., 1999).

Cerca de 95% dos casos de carcinoma de células escamosas de lábio (CCEL), podem ser precedidos por QA (LOPES et al., 2015; MARTINS-FILHO, DA SILVA, PIVA, 2011; MIRANDA et al., 2012). O CCEL é a lesão maligna mais frequente da região oral e maxilofacial, correspondendo de 25 a 30% de todos os cânceres orais (BIASOLI et al., 2016; MOORE et al., 1999). Semelhante à QA, o CCEL ocorre com maior frequência em homens brancos, porém em uma faixa etária mais elevada com maior prevalência, entre a sexta e sétima décadas de vida, e mais de 95% dos casos acomete o lábio inferior. Além das características clínicas, essas lesões também possuem em comum a exposição prolongada à luz solar como fator etiológico (DE VISSCHER et al., 1998; MELLO et al., 2019). O consumo prolongado de álcool e tabaco associado à ação carcinogênica da radiação UV aumenta consideravelmente o risco de desenvolvimento dessa neoplasia (BIASOLI et al., 2016; MOORE et al., 1999; PEREA-MILLA LÓPEZ et al., 2003). Condições sociodemográficas baixas, suscetibilidade genética e imunossupressão são outros fatores que podem contribuir (PEREA-MILLA LÓPEZ et al., 2003; VAN LEEUWEN et al., 2009). Os sinais clínicos iniciais do CCEL podem incluir crostas ou ulcerações assintomáticas que podem ser bastante equivalente ao observado nos aspectos clínicos da QA e, em estágios avançados, extensas lesões ulcerativas ou infiltrativas (BIASOLI et al., 2016; MOORE et al., 1999).

Ambas as lesões apresentam alta incidência nos países da América do Sul, principalmente nas regiões tropicais, onde há um alto nível de radiação solar e que apresentam formas de trabalho comuns nas quais os indivíduos permanecem longos períodos expostos à radiação UV (CALDEIRA et al., 2017). Embora as características e o fator etiológico principal da QA e do CCEL estejam elucidados, existem poucos estudos na América que relatam a frequência dessas lesões e os existentes são de dados locais ou regionais, ou ainda de uma população específica como trabalhadores rurais, pescadores, com amostra não representativa de todo o país.

Nesse contexto, o objetivo deste estudo multicêntrico foi determinar a frequência da QA e do CCEL entre as lesões que foram submetidas a exame histopatológico em dez centros de referência em patologia oral e maxilofacial do Brasil analisando os casos temporalmente. Adicionalmente, o perfil da amostra e as características clínicas e histopatológicas dos casos também foram estabelecidos.

1.1 Objetivos

1.1.1 Objetivos gerais

Este estudo investigou a frequência da QA e do CCEL com base nos arquivos de biópsias de centros de Patologia Oral e Maxilofacial localizados em diferentes estados do Brasil, a saber: Pará, Rio Grande do Norte, Paraíba, Pernambuco, Rio Grande do Sul, Minas Gerais, Rio de Janeiro, São Paulo e Goiás.

1.1.2 Objetivos específicos

a) Descrever o perfil dos pacientes com diagnóstico de QA e CCEL (sexo, idade, cor da pele, ocupação e hábitos);
b) Avaliar a localização mais frequente, sintomatologia, tempo de evolução das QAs e dos CCELs e o tipo de manifestação;
c) Analisar temporalmente o número de casos de QA e CCEL;
d) Avaliar histórico de QA prévia nos casos de CCEL;
e) - Analisar a presença de displasia e a gradação nos casos de QA;
f) -. Analisar o padrão de invasão nos casos de CCEL;
g) - Verificar a associação entre o grau de displasia e o padrão de invasão com as demais variáveis.

2 METODOLOGIA EXPANDIDA

2.1 Considerações éticas

O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais (Número do Parecer: 2.936.807 e CAAE: 98594918.0.1001.5149) (ANEXO A), e foi realizado de acordo com os princípios éticos Declaração de Helsinque (BELSEY, 1978).

2.2 Desenho do estudo

Este foi um estudo do tipo coorte observacional retrospectivo.

2.3 População e seleção da amostra

Foram avaliados laudos histopatológicos de biópsias de QA e CCEL. Os dados foram obtidos de 10 centros de referência de patologia oral e maxilofacial no Brasil:

a) Serviço de Patologia Oral, Hospital Universitário João de Barros Barreto, Universidade Federal do Pará (Pará). Período da análise dos casos entre 2007 a 2018;
b) Departamento de Odontologia, Programa de Pós-graduação em Patologia Oral, Universidade Federal do Rio Grande do Norte (Rio Grande do Norte). Período da análise dos casos entre 1990 a 2018;
c) Departamento de Odontologia, Universidade Estadual da Paraíba, Campina Grande (Paraíba). Período da análise dos casos entre 2011 a 2018;
d) Departamento de Cirurgia Oral e Maxilofacial e Patologia, Faculdade de Odontologia, Universidade de Pernambuco (Pernambuco). Período da análise dos casos entre 1990 a 2018;

e) Departamento de Medicina Oral, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (Rio Grande do Sul). Período da análise dos casos entre 1994 a 2018;
f) Departamento de Semiologia e Clínica, Faculdade de Odontologia, Universidade Federal de Pelotas (Rio Grande do Sul). Período da análise dos casos entre 1968 a 2018;
g) Departamento de Clínica, Patologia e Cirurgia Odontológicas, Faculdade de Odontologia, Universidade Federal de Minas Gerais (Minas Gerais). Período da análise dos casos entre 1953 a 2018;
h) Departamento de Patologia e Diagnóstico Oral, Faculdade de Odontologia, Universidade Federal do Rio de Janeiro (Rio de Janeiro). Período da análise dos casos entre 1979 a 2018;
i) Departamento de Patologia Oral e Maxilofacial, Faculdade de Odontologia, Universidade de São Paulo (São Paulo). Período da análise dos casos entre 1991 a 2018.
j) Laboratório de Patologia Bucal, Centro Goiano de Doenças da Boca, Faculdade de Odontologia, Universidade Federal de Goiás (Goiás). Período da análise dos casos entre 1999 a 2018;

2.4 Critérios de inclusão, exclusão e análise morfológica

Lesões diagnosticadas como QA ou CCEL foram incluídas no estudo. As lesões foram analisadas de acordo com os critérios de diagnósticos da QA e do CCEL de acordo com a última classificação da OMS (EL-NAGGAR *et al*., 2017). Os casos foram analisados individualmente por 10 patologistas oral e maxilofacial, um patologista de cada centro, com mais de 20 anos de experiência em diagnóstico oral e maxilofacial.

Os registros com falta de informação sobre o diagnóstico histopatológico e diagnósticos inconclusivos foram excluídos e, casos em que o diagnóstico clínico de QA não foi confirmado histopatologicamente.

2.5 Análise do perfil da amostra e características clínicas e histopatológicas

Foram avaliados sexo, idade, cor da pele (branca ou não-branca), ocupação (interna ou externa) e hábitos (fumo, consumo de álcool e exposição solar crônica). As lesões foram analisadas de acordo com a localização anatômica (lábio superior ou lábio inferior), o tempo de evolução (em meses), sintomatologia (assintomático ou sintomático), tipo de manifestação (primitiva ou recorrente) e história prévia de QA para os casos de CCEL. Histopatologicamente, foram avaliados o grau de displasia e o padrão de invasão das QAs e dos CCELs, respectivamente, de acordo com a classificação da OMS (EL-NAGGAR *et al*., 2017).

Os espécimes incluídos no estudo foram de biópsias incisionais o que impossibilitou o estabelecimento do grau de diferenciação dos CCELs.

2.6 Análise estatística

A análise dos dados foi realizada no software Statistical Package for the Social Sciences (SPSS), versão 23.0 (SPSS Inc., Chicago, IL, EUA). A estatística descritiva foi realizada para caracterizar os casos quanto ao gênero, idade, cor da pele (i.e., branca ou não-branca), ocupação (i.e., interna ou externa), hábitos (i.e., fumo, consumo de álcool e exposição solar crônica), localização anatômica (i.e., lábio superior ou lábio inferior), sintomatologia (i.e., sintomático ou assintomático), tempo de evolução (em meses), tipo de manifestação (i.e., primária ou recorrente) e história prévia de QA para os casos de CCEL.

Para a QA, o teste Qui-Quadrado foi usado para examinar a associação entre displasia e características sociodemográficas, hábitos e características clínicas. Para o CCEL, o teste do qui-quadrado também foi usado, para examinar a associação entre grau de invasão e características sociodemográficas, hábitos e características clínicas. Significância estatística foi estabelecida em $p<0,05$.

Para a QA, o teste ANOVA foi utilizado para avaliar a associação entre idade e tempo de evolução com displasia e o teste t de Student foi utilizado para avaliar a associação entre idade e tempo de evolução com sintomatologia. Para o CCEL, o teste ANOVA também foi utilizado para avaliar a associação entre idade e tempo de evolução com invasão e o teste t de Student, para avaliar a associação entre idade e

tempo de evolução com sintomatologia. A significância estatística também foi estabelecida em $p<0,05$.

3 ARTIGO

As informações e normas da revista na qual o artigo foi submetido estão contidas no Anexo B.

Clinicopathologic features of actinic cheilitis and lip squamous cell carcinoma: a Brazilian multicentre study

Running title: Actinic cheilitis & lip squamous cell carcinoma

Disclosures: None.

Conflict of interest: None.

Word count: 3,151

Keywords: actinic cheilitis; squamous cell carcinoma; precancerous conditions; lip diseases; oral diagnosis; epidemiology.

Abstract

Aims: To describe the frequency of AC and LSCC that have been submitted for microscopic examination from representative geographic regions of Brazil.

Methods and results: A retrospective multicentre study was carried out on biopsies obtained from 1953 to 2018 at 10 Brazilian Oral and Maxillofacial Pathology centres. A total of 198,709 biopsy specimens were surveyed. The sample profile and clinicopathologic characteristics were analysed. A total of 2,017 cases of ACs (1.0%) and 850 cases of LSCCs (0.4%) were recorded. A strong white (>87%) male (>70%) predilection was observed in both conditions. The mean age was 54.8±18.7 for individuals with AC and 57.8±19.0 for

individuals with LSCC. The most commonly affected site was the lower lip (>90%). There was a statistically significant association between dysplasia grade, skin colour (P=0.006) and tobacco smoking (P=0.032), and between invasion grade and tobacco smoking (P=0.004), as well as alcohol consumption (P=0.020) and previous history of AC (P=0.018).

Conclusions: This is a large multicentre study of AC and LSCC from Brazil. The frequency and clinicopathological features of AC and LSCC were similar to those described worldwide. This study provides robust and representative epidemiological data of these conditions for the scientific community.

Introduction

Actinic cheilitis (AC) is a chronic inflammatory condition that has been described as an oral potentially malignant disorder. AC affects the vermilion region of the lower lips in 95% of cases[1-3]. The occurrence of AC worldwide largely ranges between 0.9% and 43.24%[4-18]. Data from a recent systematic review and meta-analysis, in which only studies with the histopathological diagnosis of this condition were included, demonstrated the prevalence of AC at 2.08%[19]. High-risk populations, including those living in tropical regions under excessive exposure to ultraviolet (UV) radiation, fair-skinned male individuals in their forties, and smokers are the most affected by this condition[18,20,21]. Clinically, AC is characterized by dryness, fissures/erosions, atrophy (characterized by smooth, blotchy, pale areas), erythematous and/or leucoplastic areas with blurring of the margin between vermilion and the adjacent skin[2,12,22].

Nearly 95% of LSCC cases may be preceded by AC[11,30,31]; therefore, malignant transformation of AC is indeed a public health concern[32]. According to the World Health Organization (WHO)[23,24], lip squamous cell carcinoma (LSCC) is one of the most frequent malignant lesions of the oral and maxillofacial region, accounting for 25% to 30% of all oral cancers, and 12% of all head and neck cancers[22,24,25-28]. A total of 14,700 new cases of oral cancer has been estimated in Brazil in 2019[29]. However, there are no national data depicting the incidence of lip cancer in particular, since, in general, the data reported are regarded as oral cavity cancer[29]. LSCC has also predilection for fair-skinned men, with a peak incidence between the sixth and seventh decades of life. The lower lip is affected in 95% of cases. LSCC also has the prolonged exposure to sunlight as an etiological factor[2,33]. The long-term consumption of alcohol and tobacco associated with the carcinogenic action of UV radiation greatly increases the risk of developing this malignancy[28]. Sociodemographic conditions, such as social vulnerability, and genetic susceptibility, or immunosuppression, are also factors that

may contribute to the development of this disease[28,34,35]. The initial clinical signs of LSCC may include asymptomatic crusts or ulcerations that may be quite equivalent to those observed in AC. At advanced stages, a painful exudative ulcer, covered with scales and crusts, with indurated borders and infiltrated base that does not heal may take place[22,28].

Although the clinicopathological characteristics and aetiological factors of the AC and LSCC are well-studied, there are no investigations reporting representative data on these conditions of all regions of Brazil. In addition, the prevalence rates for AC and LSCC are derived from epidemiological studies with specific populations[2,11-14,17,30,31,36-40]. Considering the importance of AC and LSCC for public health, and the concern regarding the 5,898 deaths from cancer of the oral cavity in Brazil in 2015[41], the purpose of the present retrospective multicentre study was to determine the frequency of AC and LSCC in a Brazilian population from 10 different centres of oral and maxillofacial pathology. This is the largest multicentre study reporting the occurrence of these conditions in Brazil.

Materials and Methods

Study design and ethical issues

A total of 198,709 histopathological records of oral and maxillofacial biopsies were analysed in this retrospective study. The guidelines to strengthen the description of observational studies (STROBE) were followed[42]. The records were obtained from a consortium of 10 referral centres of oral and maxillofacial pathology across the five Brazilian regions: North, North-East, South, South-East and Midwest. The specimens included in the study were from incisional biopsies, which made it impossible to establish the degree of differentiation of LSCCs. This multicentre study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais (No. 2.936.807 and No. 98594918.0.1001.5149). Patient's anonymity was ensured in conformity with the Declaration of Helsinki of 1964.

Clinical and histopathological data

A total of 2,017 biopsy records of AC and 850 of LSCC were retrieved. Affected individuals were analysed concerning gender, age (mean ± standard deviation and decades of life), skin colour (white/non-white), occupation (indoor/outdoor) and habits (tobacco smoking, alcohol consumption and chronic solar exposure). Lesions were analysed in terms of anatomical location (upper/lower lip), evolution time in month(s), symptoms (symptomatic/asymptomatic), manifestation type (primitive/recurrent), and previous history of AC for cases of LSCC. For AC cases, grade of epithelial dysplasia (mild, moderate or severe) was evaluated. For cases of LSCC, invasion pattern (*in situ*, superficially invasive or invasive) was also analysed.

The grade of AC and LSCC were classified in consonance with the 2017 classification of the WHO[23]. The cases were investigated individually by 10 oral and maxillofacial pathologists with more than 20 years of experience. Records with lack of specific information regarding histopathological diagnosis of AC and LSCC were excluded.

Data analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 23.0 (SPSS Inc., Armonk, NY, USA). Descriptive statistics was carried out to characterise the cases regarding patient's sample profile (gender, age, skin colour and occupation), habits (tobacco smoking, alcohol consumption and chronic solar exposure) as well as clinical and histopathological features (symptoms, anatomical location, evolution time, type of manifestation, previous history of AC for cases of LSCC, and histopathological patterns).

For AC, the Chi-Square test was used to examine the association between dysplasia grade and sample profile, habits as well as clinical features. For LSCC, the Chi-Square test was also used to examine the association between invasion pattern and sample profile, habits as well as clinical features. For AC, the Student-*t* test was used to evaluate the association of age and evolution time with dysplasia grade and symptomatology. For LSCC, the Student-*t* test was also used to evaluate the association of age and evolution time with invasion pattern and symptomatology. The Kolmogorov-Smirnov test showed that the quantitative variables presented non-normal distribution. For all tests, statistical significance was set at $P<0.05$.

Results

A total of 198,709 histopathological records of oral and maxillofacial biopsies had been diagnosed at the 10 centres; of these, 2,017 were cases of AC (1.0%) and 850 were cases of LSCC (0.4%). The distribution of AC and LSCC cases by centre is depicted in Table 1. General data on sample profile and clinicopathological features of cases of AC and LSCC are shown in Table 2. Figure 1 displays the temporal distribution of cases of AC and LSCC cases per decade. Variable percentages were calculated by the number of data reported excluding missing data.

Data of individuals with AC

A total of 1,439 (71.4%) cases occurred in males and 575 (28.6%) in females (male-to-female ratio of 2.5:1). Elderlies (≥60 years) accounted for 49.8% of the survey. Most individuals were whites (87.3%), reported an indoor occupation (56.6%) and had no symptoms (78.8%). Of the individuals who had answered positively for the habits of tobacco

smoking, alcohol consumption and chronic solar exposure, 75.5% were smokers, 91.7% were alcohol users and 91.5% were chronically exposed to the sun.

The most common site of the AC was the lower lip (98.7%) and 87.2% presented as a primary manifestation with a median evolution time of 12 months. Figure 2 represents the main clinical features of Brazilian individuals with AC. Epithelial dysplasia was observed in 66.8% of the cases; of these, 31.5% were mild, 28% were moderate and 7.3% were severe. Figure 4 shows the main histopathological aspects of AC cases. In 55.1% of the cases, the histopathological diagnosis confirmed the clinical diagnosis of AC. The other clinical diagnostic hypotheses were oral leukoplakia (25.2%) and oral squamous cell carcinoma (5.6%).

Data of individuals with LSCC

A total of 673 (79.3%) cases occurred in males and 176 (20.7%) in females (male-to-female ratio of 3.8:1). The majority of cases consisted of elderly individuals (54.2%), whites (91.3%), those whose occupation was indoor (56.9%) and asymptomatic (63.3%). Of the individuals who had reported on the habits evaluated, 67.6% were smokers, 50.5% were alcohol users and 83.5% were chronically exposed to the sun.

The lower lip was also the most common anatomical location of the LSCC (97.3%). Figure 3 represents the main clinical features of Brazilian individuals with LSCC. Regarding the type of manifestation, 94.2% of the lesions were primary and 91.5% did not present a previous history of AC. The median follow-up time was 12 months. Regarding the invasion pattern in the lesions, 82.9% were invasive, 10.2% were superficially invasive and 6.9% were *in situ*. Figure 4 shows the main histopathological aspects of LSCC cases. In 74.2% of the

cases, the histopathological diagnosis confirmed the clinical diagnosis of LSCC. The other clinical diagnostic hypotheses were AC (11.5%) and oral leukoplakia (4.4%).

Association among sociodemographic characteristics and clinical features with dysplasia grade of AC and invasion pattern of LSCC

Regarding the degree of epithelial dysplasia of AC, the associations with skin colour (*P*=0.006) and tobacco smoking (*P*=0.032) were statistically significant. Cases of AC from individuals who were non-smokers presented no epithelial dysplasia. Smokers and former smokers presented dysplasia in some degree. Regarding the invasion pattern of LSCC, tobacco smoking (*P*=0.004), alcohol consumption (*P*=0.020) and previous history of AC (*P*=0.018) were statistically significant. Sixty-eight individuals who had previous AC, the LSCC was invasive (Table 3).

Significant differences were observed in the comparisons between dysplasia grade with evolution time of AC (*P*=0.026), as well as invasion pattern with evolution time of LSCC (*P*=0.002) (Table 4).

Discussion

AC has been widely studied and its clinical importance stands out due to the possibility of malignant transformation of this disorder to lip cancer[32]. Brazilian investigations have demonstrated the frequency of AC ranging from 0.4 to 8.4%[2,6,9,17,43]. For LSCC, the occurrence varies between 1.27 and 5.3 in 100,000 individuals annualy[25,44-47]. Nevertheless, most investigations about AC are observational studies or case series, in which the diagnosis of such condition was based exclusively on clinical parameters. Furthermore, these studies are

restricted to specific populations of individuals exposed constantly to the aetiological factor (UV radiation), such as rural workers, sugarcane workers, beach workers and fishermen. The findings of these studies should also be interpreted with caution due to the assessments carried out in a particular city or state of the country[2,7-14,17,18,26-28,30,33,37,40]. Therefore, comparisons with the results of our study are worth doing, but should be made attentively since this is the first evaluation of a representative survey of AC and LSCC that have been submitted for microscopic examination from all regions of Brazil, depicting sample profile and clinicopathologic aspects of these conditions. Interestingly, an increase in the number of cases of AC and LSCC over the last decades, mainly in the years of 2000 has been observed. Indeed, these outcomes may have occurred due to the expansion of access to dental care and the intensification of oral cancer prevention campaigns on early diagnosis throughout the country[48-51].

Regarding sample profile on AC and LSCC, the findings obtained herein are in accordance with previous reports, showing a high frequency among white men. In line with the literature, nearly 82% of AC cases and 80% of LSCC cases have affected men, whereas 85% of individuals with AC and 87% of individuals with LSCC are white individuals[2]. These features strengthen the statement that white individuals are more susceptible to the development of diseases, whose etiological factor is UV radiation, because of the lower amount of melanin present in their skin[32,36,52]. Moreover, tropical countries such as Brazil, where a large number of male individuals work in outdoor occupations or have the habit of prolonged exposure to UV radiation tend to have a greater number of cases of these lesions due to high solar incidence and not use of protective agents such as sunscreen and hat. [27,53-55]. However, cases of AC have been reported predominantly among black individuals in Africa and no imbalance in the male to female ratio has been observed[56].

Individuals affected by AC and LSCC are usually middle-aged or elderly individuals, with a mean age higher than 40 years[2,22,27,28,52]. Few studies have reported cases of young people affected by LSCC[57,58]. Moreover, there is a difference in the age at diagnosis between individuals with AC and individuals with LSCC. Cases of LSCC have been diagnosed at a later age (sixth and seventh decades of life)[22,25-28,33,34] when compared to cases of AC (fifth decade of life) showing the chronic character of the acquisition of the malignant phenotype [2,18,22,55]. Our findings are in contrast with the findings of the aforementioned reports, in which there is highest concentration of diagnosis among individuals between the sixth and eighth decades of life suggesting a late diagnosis in cases of AC. These data reinforce the increasing need for the continuity and broadening of campaigns for the prevention and early diagnosis of these lesions, thus reducing the neglect of AC by the population by disseminating knowledge about the importance of prevention this lesion and the search for a professional for diagnosis and treatment.

As regards the occupation of individuals, previous studies have reported that the prevalence of AC and LSCC is higher among individuals with outdoor occupations[11,18,25,26,28,31,33,59]. Herein, most affected individuals with AC and LSCC presented indoor occupations. These findings seem paradoxical, but may be justified. Nearly 25% of individuals who provided information on their occupation were retired, unemployed or were housewives. Outdoor occupation not only contributes to the appearance and progression of these lesions, but may also encourage the individuals in the development of habits, such as smoking, alcohol consumption and chronic exposure to the sun, regardless of their occupation[2,22,25,28,45]. Although many individuals in the present study had not reported data regarding habits; among those who reported, the frequency of habits was quite high, with more than 75% of the individuals, confirming they were smokers and more than 90% reporting alcohol consumption. In line with this, in other investigations, these high rates were

also observed[2,58,60]. In addition, the association of the primary aetiological factor (UV radiation) with secondary factors, such as smoking and/or alcohol consumption is still unclear. In some studies, smoking has been suggested as one of the main secondary factors for the development of LSCC[33,34,47,61]. Therefore, further studies are needed to clarify the potential contribution of tobacco and alcohol consumption to LSCC aetiopathogenesis[60].

In our study, although the association between dysplasia grade and tobacco smoking demonstrated a higher percentage of smokers presenting mild dysplasia grade, the association between habits and invasion exhibited a higher frequency of cases of invasive carcinoma among individuals who were smokers and alcohol consumers, confirming the role of habits on the development of this lesion[61]. Another significant association observed in the current study, was of dysplasia grade and invasion pattern with evolution time. The more severe the dysplasia grade and invasion pattern, the shorter the evolution time of the disease. Thus, LSCC may have a greater aggressiveness and consequently rapid evolution among individuals, who presented a more severe dysplasia or invasion pattern. A significant association between invasion pattern and previous history of AC was also observed. Individuals, who had a history of previous AC presented invasive carcinomas, suggesting disease progression and even a higher invasion pattern of LSCC. Abreu *et al*.[62] also suggested that in cases in which AC was not observed adjacent to LSCC, there is a possibility that focal AC was the starting point for malignancy. Moreover, the presence of adjacent solar elastosis would indicate a prior history of AC at the site, although the presence of AC adjacent to the tumor may be an indication of better prognosis for the case[62]. In particular situations, the reality of the clinical aspects does not correspond to the severity of the microscopic findings[63]. In this regard, caution should be taken when interpretations with respect to the behaviour of the lesions are based solely on statistical results.

With respect to the most frequent anatomical site of the lesions studied herein, the lower lip is undoubtedly the most affected, with a rate of almost 95% of the cases reported[2,11,18,20,22,28,43]. The present study reinforces these findings, since more than 97% of the cases were in the lower lip. Though visible, these early-stage lesions are often neglected due to the lack of symptoms in most cases[22,32]. In this study, there was a high frequency of individuals with AC or LSCC who were asymptomatic. Absence of symptoms is relevant information for the clinical diagnosis of AC and LSCC. In nearly 55% of cases of AC and 74% of LSCC, clinical diagnosis was confirmed histopathologically, similarly reported by Melo *et al.*[2]. Thus, this data pool reinforces the importance of the knowledge on these lesions by clinicians and dermatologists, who should be concerned with early diagnosis and timely referral to adequate treatment[51]. The evolution time of these lesions is slow[32,64], demonstrating a potential for malignant transformation and a much lower aggression pattern when compared to other lesions, such as intraoral erythroplakia and carcinoma of the oral cavity[3,19,32,43,65]. Although the study conducted by Kaugars *et al.*[66] showed no difference in the pattern of differentiation and invasion between primary and recurrent cases, definitive conclusions are limited by the low number of cases analyzed[66].

Our study also provides useful information regarding the histological aspects of the lesions studied. Of the cases of AC, in which some degree of dysplasia was observed, most cases presented mild dysplasia (31.5%), corroborating the findings of Kaugars *et al.*[66] and Mello et al.[2], but contrasting with the findings of the study of Cavalcante *et al.*[36], whose participants predominantly presented severe epithelial dysplasia (62%)[36]. For the LSCC cases, was verified a higher frequency of invasive carcinoma, and this is important because the LSCC yet is diagnosed in late stage.

The present study has limitations that should be recognized. The first is the retrospective design of the study with participants recruited in secondary care facilities. Thus,

it was impossible to follow the clinical course of the individuals, to analyse the rate of malignant transformation of AC, and to obtain the degree of differentiation and the survival rate in the cases of LSCC. Regarding the malignant transformation rate of AC, the literature is quite controversial. The studies did not use the same methodology to estimate this rate and no certainty on the progression of AC to LSCC exists[32]. A rate of 3.07% has been reported in a systematic review[32]. However, no meta-analysis has been available and the estimate was determined in a single study included in the cited review[32]. On the other hand, information on LSCC survival rate is well-documented in the literature[58,67-70]. Individuals affected by this malignancy have higher survival rates when compared to individuals with other head and neck cancers[71-73], due to the anatomical location and the clinical behaviour. The five-year survival rate for patients diagnosed with LSCC ranges from 62% to 81%[59,71,74].

In summary, data of the Brazilian individuals with AC and LSCC reported herein agree with findings of case series and retrospective studies reported elsewhere. There is a predilection of white men in their seventh decade of life (mean age between 54 and 57 years). In most cases, the lower lip is affected. There was a significant association of smoking habit with the dysplasia grade in AC and invasion pattern in LSCC cases. There was also a significant association of alcohol consumption with invasion pattern in LSCC cases.

Abbreviations:

AC: Actinic cheilitis

UV: Ultraviolet

WHO: World Health Organization

LSCC: Lip squamous cell carcinoma

SPSS: Statistical Package for the Social Sciences

Contributions of author:

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References

1. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med 2007; 36: 575-580.
2. Mello FW, Melo G, Modolo F, Rivero ER. Actinic cheilitis and lip squamous cell carcinoma: Literature review and new data from Brazil. J Clin Exp Dent 2019; 11: 62-69.
3. Warnakulasuriya S. Clinical features and presentation of oral potentially malignant disorders. Oral Surg Oral Med Oral Pathol Oral Radiol 2018; 125: 582-590.
4. Jorge Júnior J, de Almeida OP, Bozzo L et al. Oral mucosal health and disease in institutionalized elderly in Brazil. Community Dent Oral Epidemiol 1991; 19: 173-175.
5. Campisi G, Margiotta V. Oral mucosal lesions and risk habits among men in an Italian study population. J Oral Pathol Med 2001; 30: 22-28.
6. Espinoza I, Rojas R, Aranda W, Gamonal J. Prevalence of oral mucosal lesions in elderly people in Santiago, Chile. J Oral Pathol Med 2003; 32: 571-575.
7. Silva FD, Daniel FI, Grando LJ et al. Study of the prevalence of lip alterations in fisherman from Santa Catarina island. Rev Odonto Ciênc 2006; 21: 239-244.
8. Zanetti R, Flório FM, Moraes PC et al. Prevalence of actinic cheilitis in an oral health campaign in the city of Campinas, SP. J Appl Oral Sci 2007; 15: 353.
9. Henrique PR, Júnior MB, Araújo VCD et al. Prevalência de alterações da mucosa bucal em indivíduos adultos da população de Uberaba, Minas Gerais. RGO: Revista Gaúcha de Odontologia 2009; 57.

10. Miranda AM, Ferrari TM, Calandro TLL. Queilite actínica: aspectos clínicos e prevalência encontrados em uma população rural no interior do Brasil. Rev Saúde Pesq 2011; 4: 67-72.
11. Martins-Filho PR, Da Silva LC, Piva MR. The prevalence of actinic cheilitis in farmers in a semi-arid northeastern region of Brazil. Int J Dermatol 2011; 50: 1109-1114.
12. Junqueira JL, Bönecker M, Furuse C et al. Actinic cheilitis among agricultural workers in Campinas, Brazil. Community Dent Health 2011; 28: 60-63.
13. de Souza Lucena EE, Costa DC, da Silveira EJ, Lima KC. Prevalence and factors associated to actinic cheilitis in beach workers. Oral Dis 2012; 18: 575-579.
14. de Oliveira Ribeiro A, da Silva LC, Martins-Filho PR. Prevalence of and risk factors for actinic cheilitis in Brazilian fishermen and women. Int J Dermatol 2014; 53: 1370-1376.
15. Gheno JN, Martins MA, Munerato MC et al. Oral mucosal lesions and their association with sociodemographic, behavioral, and health status factors. Braz Oral Res 2015; 29: pii: S1806-83242015000100289.
16. Silva MF, Barbosa KG, Pereira JV et al. Prevalence of oral mucosal lesions among patients with diabetes mellitus types 1 and 2. An Bras Dermatol 2015; 90: 49-53.
17. Ferreira AM, de Souza Lucena EE, de Oliveira TC et al. Prevalence and factors associated with oral potentially malignant disorders in Brazil's rural workers. Oral Dis 2016; 22: 536-542.
18. Rodríguez-Blanco I, Flórez Á, Paredes-Suárez C et al. Actinic Cheilitis Prevalence and Risk Factors: A Cross-sectional, Multicentre Study in a Population Aged 45 Years and Over in North-west Spain. Acta Derm Venereol 2018; 98: 970-974.

19. Mello FW, Miguel AFP, Dutra KL et al. Prevalence of oral potentially malignant disorders: A systematic review and meta-analysis. J Oral Pathol Med 2018; 47: 633-640.
20. Markopoulos A, Albanidou-Farmaki E, Kayavis I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. Oral Dis 2004; 10: 212-216.
21. Salgueiro AP, de Jesus LH, de Souza IF et al. Treatment of actinic cheilitis: a systematic review. Clin Oral Investig 2019; 23: 2041-2053.
22. Vieira RA, Minicucci EM, Marques ME, Marques SA. Actinic cheilitis and squamous cell carcinoma of the lip: clinical, histopathological and immunogenetic aspects. An Bras Dermatol 2012; 87: 105-114.
23. El-Naggar AK, Chan JKC, Grandis JR et al. WHO Classification of Head and Neck Tumours, 4th edn. Lyon: IARC Press, 2017.
24. Ferlay J, Colombet M, Soerjomataram I et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019; 144:1941-1953.
25. Moore SR, Johnson NW, Pierce AM et al. The epidemiology of lip cancer: a review of global incidence and aetiology. Oral Dis 1999; 5: 185-195.
26. Luna-Ortiz K, Güemes-Meza A, Villavicencio-Valencia V et al. Lip cancer experience in Mexico. An 11-year retrospective study. Oral Oncol 2004; 40: 992-999.
27. Kornevs E, Skagers A, Tars J et al. 5 year experience with lower lip cancer. Stomatologija 2005; 7: 95-98.
28. Biasoli ÉR, Valente VB, Mantovan B et al. Lip Cancer: A Clinicopathological Study and Treatment Outcomes in a 25-Year Experience. J Oral Maxillofac Surg 2016; 74: 1360-1367.

29. Brasil. Ministério da Saúde. Instituto Nacional de Câncer. Estimativa 2019: incidência de câncer no Brasil. Rio de Janeiro: INCA. 2018; 39.
30. Miranda AM, Soares LG, Ferrari TM et al. Prevalence of actinic cheilitis in a population of agricultural sugarcane workers. Acta Odontol Latinoam 2012; 25: 201-206.
31. Lopes ML, Silva Júnior FL, Lima KC et al. Clinicopathological profile and management of 161 cases of actinic cheilitis. An Bras Dermatol 2015; 90: 505-512.
32. Dancyger A, Heard V, Huang B et al. Malignant transformation of actinic cheilitis: A systematic review of observational studies. J Investig Clin Dent 2018; 9: 12343.
33. de Visscher JG, Schaapveld M, Otter R et al. Epidemiology of cancer of the lip in The Netherlands. Oral Oncol 1998; 34: 421-426.
34. Perea-Milla López E, Miñarro-Del Moral RM, Martínez-García C et al. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case-control study in southern Spain. Br J Cancer 2003; 88: 1702-1707.
35. van Leeuwen MT, Grulich AE, McDonald SP et al. Immunosuppression and other risk factors for lip cancer after kidney transplantation. Cancer Epidemiol Biomarkers Prev 2009; 18: 561-569.
36. Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: clinical and histological features. J Oral Maxillofac Surg 2008; 66: 498-503.
37. Piñera-Marques K, Lorenço SV, Silva LF et al. Actinic lesions in fishermen's lower lip: clinical, cytopathological and histopathologic analysis. Clinics (Sao Paulo) 2010; 65: 363-367.
38. Sarmento DJ, Godoy GP, Miguel MC, Silveira ÉJ. Link between immunoexpression of hMLH1 and hMSH2 proteins and clinical-epidemiological aspects of actinic cheilitis. An Bras Dermatol 2016; 91: 463-467.

39. Poitevin NA, Rodrigues MS, Weigert KL et al. Actinic cheilitis: proposition and reproducibility of a clinical criterion. BDJ Open 2017; 3: 17016.

40. Santos RFD, Oliveira RL, Gallottini M et al. Prevalence of and Factors Associated with Actinic Cheilitis in Extractive Mining Workers. Braz Dent J 2018; 29: 214-221.

41. BRASIL. Ministério da Saúde. Departamento de Informática do SUS. Sistema de informações sobre mortalidade. Brasília, DF, 2017. Available at: http://www.datasus.gov.br/DATASUS/index.php?area=060701 Accessed in June 2, 2019.

42. Knottnerus A, Tugwell P. STROBE—a checklist to strengthen the reporting of observational studies in epidemiology. J Clin Epidemiol 2008; 61: 323.

43. Silveira ÉJD, Lopes MFF, Silva LMM et al. Potentially malignant oral lesions: clinical and morphological analysis of 205 cases. J Bras Patol Med Lab 2009; 45: 233-238.

44. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2008; 17: 309-316.

45. Abreu L, Kruger E, Tennant M. Lip cancer in Western Australia, 1982-2006: A 25-year retrospective epidemiological study. Aust Dent J 2009; 54: 130-135.

46. Videnović G, Illić D, Miljus D et al. Lip, oral cavity and pharyngeal cancers in the population of the city of Belgrade in the period 1999-2010. Vojnosanit Pregl 2016; 73: 53-58.

47. Jadotte YT, Schwartz RA. Solar cheilosis: an ominous precursor: part I. Diagnostic insights. J Am Acad Dermatol. 2012; 66: 173-184.

48. Martins JS, Abreu SC, Araújo ME et al. [Strategies and results of the oral cancer prevention campaign among the elderly in São Paulo, Brazil, 2001 to 2009]. Rev Panam Salud Publica 2012; 31: 246-252.

49. Baumann E, Koller M, Wiltfang J et al. Challenges of early detection of oral cancer: raising awareness as a first step to successful campaigning. Health Educ Res 2016; 31: 136-145.
50. Cruz-Moreira K, Huamán-Garaicoa F, Mena G. Knowledge of oral cancer among the community served during the stomatological lesion prevention campaign conducted at Universidad Católica de Santiago de Guayaquil - Ecuador. Acta Odontol Latinoam 2017; 30: 113-117.
51. MacCarthy D, McAlister C, O'Sullivan E. Campaign for awareness of cancer of the head and neck in Ireland. Br J Oral Maxillofac Surg 2017; 55: 213-214.
52. Maruccia M, Onesti MG, Parisi P et al. Lip cancer: a 10-year retrospective epidemiological study. Anticancer Res 2012; 32: 1543-1546.
53. Corrêa MP. Solar ultraviolet radiation: properties, characteristics and amounts observed in Brazil and South America. An Bras Dermatol 2015; 90: 297-313.
54. Caldeira PC, Silva LS, Batista AC, Aguiar MC. Thioredoxin and metallothionein: Homeostasis-related proteins in lip carcinogenesis. Arch Oral Biol 2017; 77: 75-81.
55. De Santana Sarmento DJ, da Costa Miguel MC, Queiroz LM et al. Actinic cheilitis: clinicopathologic profile and association with degree of dysplasia. Int J Dermatol 2014; 53: 466-472.
56. Goracci G, Colangelo G, Nini G. [Incidence of actinic cheilitis in Somalia]. Riv Ital Stomatol 1981; 50: 1009-1016.
57. Chidzonga MM. Lip cancer in Zimbabwe. Report of 14 cases. Int J Oral Maxillofac Surg 2005; 34: 149-151.
58. Salihu S, Güven O, Gllareva E, Prekazi M, Salihu L. A clinical study on survival rate of patients with squamous cell carcinoma of the lower lip in Kosovo. J Craniomaxillofacl Surg 2014; 42: 1773-1777.

59. .Czerninski R, Zini A, Sgan-Cohen H. Lip cancer: incidence, trends, histology and survival: 1970–2006. Br J Dermatol 2010; 162: 1103-1109.
60. Souza LR, Fonseca-Fonseca T, Oliveira-Santos CC et al. Lip squamous cell carcinoma in a Brazilian population: Epidemiological study and clinicopathological associations. Med Oral Patol Oral Cirug Bucal 2011; 16: 757-762.
61. Figuero Ruiz E, Carretero Peláez MA, Cerero Lapiedra R, Esparza Gómez G, Moreno López LA. Effects of the consumption of alcohol in the oral cavity: relationship with oral cancer. Med Oral 2004; 9: 14-23.
62. Abreu MA, Silva OM, Neto Pimentel DR et al. Actinic cheilitis adjacent to squamous carcinoma of the lips as an indicator of prognosis. Braz J Otorhinolaryngol 2006; 72: 767-771.
63. Nico MMS, Rivitti EA, Lourenco SV. Actinic cheilitis: histologic study of the entire vermilion and comparison with previous biopsy. J Cutan Pathol 2007; 34: 309-314.
64. Bozan N, Kocak OF, Cankaya H et al. Lip cancer: A 16-year retrospective epidemiological study in Eastern part of Turkey. J Pak Med Assoc 2016; 66: 1433-1435.
65. Batista AC, Costa NL, Oton-Leite AF, Mendonca EF, Alencar RC, Silva TA. Distinctive clinical and microscopic features of squamous cell carcinoma of oral cavity and lip. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 109: 74-79.
66. Kaugars GE, Pillion T, Svirsky JA, Page DG, Burns JC, Abbey LM. Actinic cheilitis: a review of 152 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 88: 181-186.
67. Olaleye O, Ekrikpo U, Lyne O, Wiseberg J. Incidence and survival trends of lip, intra-oral cavity and tongue base cancers in south-east England. Ann R Coll Surg Engl 2015; 97: 229-234.

68. Cabello BT, Sazo BN, Salgado FA, Martínez RB. [Squamous cell carcinoma of the lip survival rate]. Rev Med Chil 2015; 143: 847-855.
69. Chen SW, Zhang Q, Guo ZM et al. Trends in clinical features and survival of oral cavity cancer: fifty years of experience with 3,362 consecutive cases from a single institution. Cancer Manag Res 2018; 10: 4523-4535.
70. Agostini T, Spinelli G, Arcuri F, Perello R. Metastatic Squamous Cell Carcinoma of the Lower Lip: Analysis of the 5-Year Survival Rate. Arch Craniofac Surg 2017; 18: 105-111.
71. Guntinas-Lichius O, Wendt T, Buentzel J et al. Head and neck cancer in Germany: a site-specific analysis of survival of the Thuringian cancer registration database. J Cancer Res Clin Oncol 2010; 136: 55-63.
72. Jehn P, Dittmann J, Zimmerer R et al. Survival Rates According to Tumour Location in Patients With Surgically Treated Oral and Oropharyngeal Squamous Cell Carcinoma. Anticancer Res 2019; 39: 2527-2533.
73. Yao JJ, Qi ZY, Liu ZG et al. Clinical features and survival outcomes between ascending and descending types of nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: A big-data intelligence platform-based analysis. Radiother Oncol 2019; 137: 137-144.
74. Sargeran K, Murtomaa H, Safavi SMR, Vehkalahti MM, Teronen O. Survival after lip cancer diagnosis. J Craniofac Surg 2009; 20: 248-252.

Figure legends

Figure 1. Temporal distribution of cases of actinic cheilitis (AC) and lip squamous cell carcinoma (LSCC) cases per decade.

Figure 2. Clinical features of actinic cheilitis. In all cases is observed the blurring of the margin between the vermilion border of the lower lip. **(a)** Atrophic regions, oedema, and pigmented areas. **(b)** Small ulcer in the central region of the lower lip. **(c)** Leucoplastic and pigmented areas in the lower lip. **(d)** Swollen lesion with atrophic and leucoplastic. **(e)** Erythematous and leucoplastic regions with oedema. **(f)** Ulcerated, crusty and leucoplastic lesions with presence of oedema. **(g)** Crusty lesions along the border of the vermilion of the upper and lower lip, as well as ulcer and oedema adjacent to the crust on the left side of the lower lip. **(h)** Presence of exuberant ulcer in central region of the lower lip with leucoplastic border.

Figure 3. Clinical features of lip squamous cell carcinoma cases. (a) A small ulceration of the lower lip vermillion mimicking an actinic cheilitis. Note lesions with crust and ulceration, presence of atrophic regions, oedema, and blurring of the margin between the vermilion and the adjacent skin. **(b)** Ulcerated and crusty lesions with blurring of the margin between the vermillion and adjacent skin. **(c)** Ulcerated and swollen lesion with crusted and atrophic areas with blurring of the margin between the vermillion and adjacent skin. **(d)** Presence of a crusted lesion with areas of atrophy oedema and blurring of the margin between the vermilion and the adjacent skin. **(e)** Ulcerated lesion in the central region of the lower lip with presence of oedema. **(f)** Presence of exuberant ulcer with leucoplastic border, raised and hardened and beginning of crust formation on the lesion.

Figure 4. (a) Histopathology of the actinic cheilitis: hyperkeratosis, epithelial atrophy, basal cell hyperplasia, discrete nuclear hyperchromatism and pleomorphism. In connective tissue is observed basophilic degeneration of collagen fibers (solar elastosis) (H&E staining, 10x magnification). **(b)** Histopathology of lips squamous cell carcinoma: shows invasive islands of malignant squamous epithelial cells presented severe nuclear and cellular pleomorphism, increased nucleus-cytoplasm ratio and evident nucleolus (H&E staining; x400 magnification).

Table 1. Information regarding the sources of the reviewed cases of actinic cheilitis (AC) and lip squamous cell carcinoma (LSCC)

Centre	State	Population (million)	Period	Number of biopsied lesions	AC (n)	AC (%)[b]	LSCC (n)	LSCC (%)[b]
UFPA[c]	Pará	8,513,497	2007-2018	5,689	25	0.4	19	0.3
UFRN[d]	Rio Grande do Norte	3,479,010	1990-2018	12,528	207	1.6	43	0.3
UPE[e]	Pernambuco	9,496,294	1990-2018	6,911	42	0.6	11	0.2
UEPB[f]	Paraíba	3,996,496	2011-2018	3,112	83	2.7	26	0.8
UFPel[g]	Rio Grande do Sul	11,329,605	1968-2018	24,910	218	0.9	341	1.4
UFRGS[h]	Rio Grande do Sul	11,329,605	1994-2018	NA[m]	125	-[n]	197	-[n]
USP[i]	São Paulo	12,176,866	1991-2018	82,406	965	1.2	NA[o]	-[p]
UFMG[j]	Minas Gerais	21,040,662	1953-2018	37,363	200	0.5	113	0.3
UFRJ[k]	Rio de Janeiro	17,159,960	1979-2018	15,232	75	0.5	65	0.4
UFG[l]	Goiás	6,921,161	1999-2018	10,558	77	0.7	35	0.3
Total	**-**	**-**	**-**	**198,709**	**2,017**	**1.0**	**850**	**0.4**

[a]Data according to the Brazilian Institute of Geography and Statistics (IBGE, 2018). [b]Percentage of the whole sample. [c]Service of Oral Pathology, Hospital Universitário João de Barros Barreto, Universidade Federal do Pará (North region). [d]Post-Graduation Program in Oral Pathology of the Universidade Federal do Rio Grande do Norte (North-East region). [e]Department of Oral and Maxillofacial Surgery and Pathology, School of Dentistry, Universidade de Pernambuco (North-East region). [f]Department of Dentistry, School of Dentistry of the Universidade Estadual da Paraíba (North-East region). [g]Diagnostic Centre for Oral Diseases of the Universidade Federal de Pelotas (South region). [h]Department of Oral Medicine, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (South region). [i]Department of Oral and

Maxillofacial Pathology, School of Dentistry of Universidade de São Paulo (South-East region). [j]Department of Oral Surgery and Pathology, School of Dentistry of the Universidade Federal de Minas Gerais (South-East region).[k]Department of Oral Diagnosis and Pathology, School of Dentistry of the Universidade Federal do Rio de Janeiro (South-East region).[l]Department of Stomatology (Oral Pathology), School of Dentistry of the Universidade Federal de Goiás (Midwest region).[m]Data are not available (NA) because the data are from a primary centre, therefore, lesions affecting the maxillofacial region are not separated from the others. [n]Data not calculated by the absence of the total number of biopsied lesions. [o]Data from this lesion were not collected at this centre. [p]Data not calculated by the absence of the number of LSSC lesions.

Table 2. Sample profile, habits, clinical and histopathological features of the individuals with actinic cheilitis (AC) and lip squamous cell carcinoma (LSCC)

	AC number (%)	LSCC number (%)
Gender		
Male	1,439/2,014 (71.4)	673/849 (79.3)
Female	575/2,014 (28.6)	176/849 (20.7)
Age (years/decades)	1,913; mean: 54.8±18.7; range: 3-100	811; mean: 57.8±19.0; range: 7-103
0-9	3 (0.2)	2 (0.2)
10-19	7 (0.4)	2 (0.2)
20-29	57 (3.0)	14 (1.7)
30-39	142 (5.6)	52 (6.4)
40-49	276 (14.4)	93 (11.5)
50-59	475 (24.8)	208 (25.6)
60-69	570 (29.8)	222 (27.4)
70-79	309 (16.2)	150 (18.5)
80-89	67 (3.5)	58 (7.2)
90-99	5 (0.3)	7 (0.9)
100-109	1 (0.1)	3 (0.4)
Skin colour		
White	1,640/1,879 (87.3)	726/795 (91.3)
Non-white	239/1,879 (12.7)	69/795 (8.7)
Symptoms		
Symptomatic	177/1,218 (21.2)	62/169 (36.7)
Asymptomatic	1041/1,218 (78.8)	107/169 (63.3)
Anatomical location		
Upper lip	27/2,017 (1.3)	23/850 (2.7)
Lower lip	1990/2,017 (98.7)	827/850 (97.3)
Occupation		
Indoor	404/714 (56.6)	329/578 (56.9)
Outdoor	310/714 (43.4)	249/578 (43.1)
Evolution time (months)	1,018; median: 12; range: 0.25-600	459; median: 12; range: 0.25-720
Dysplasia grade[a]		
Mild	331/1052 (31.5)	-
Moderate	295/1052 (28.0)	-

Severe	77/1052 (7.3)	-
Absent	349/1052 (33.2)	-
Invasion pattern[b]		
In situ	-	59/850 (6.9)
Superficially invasive	-	86/850 (10.2)
Invasive	-	705/850 (82.9)
Previous history of AC[c]		
Yes	-	72/850 (8.5)
NA	-	778/850 (91.5)
Manifestation type		
Primary	735/843 (87.2)	685/727 (94.2)
Recurrent	108/843 (12.8)	42/727 (5.8)
Habits		
Tobacco smoking		
Yes	80/106 (75.5)	121/179 (67.6)
No	3/106 (2.8)	24/179 (13.4)
Ex-smoker	23/106 (21.7)	34/179 (19.0)
Alcohol consumption		
Yes	33/36 (91.7)	49/97 (50.5)
No	0/36 (0.0)	23/97 (23.7)
Ex-consumer	3/36 (8.3)	25/97 (25.8)
Chronic solar exposure		
Yes	75/82 (91.5)	91/109 (83.5)
No	7/82 (8.5)	18/109 (16.5)

[a]This variable does not apply to LSCC.
[b]This variable does not apply to AC.
[c]This variable does not apply to AC.
NA, not available.

Table 3. Association among sample profile, habits and clinical features with dysplasia grade of actinic cheilitis (AC) and invasion pattern of lip squamous cell carcinoma (LSCC)

	AC dysplasia (%)				*P*-value[a]	LSCC invasion (%)			*P*-value[a]
	Mild	**Moderate**	**Severe**	**Absent**		***in situ***	**Superficially invasive**	**Invasive**	
Gender									
Male	256 (33.5)	203 (26.6)	52 (6.8)	253 (33.1)	0.095	41 (6.1)	72 (10.7)	560 (83.2)	0.161
Female	75 (26.2)	90 (31.5)	25 (8.7)	96 (33.6)		17 (9.7)	14 (7.9)	145 (82.4)	
Skin colour									
White	224	213	60	280	**0.006***	52 (7.2)	76 (10.5)	598 (82.4)	0.182
Non-white	71	51	10	44		2 (2.9)	3 (4.3)	64 (92.8)	
Occupation									
Indoor	138 (34.2)	116 (28.7)	31 (7.7)	119 (29.5)	0.926	27 (8.2)	37 (11.2)	265 (80.6)	0.638
Outdoor	113 (36.5)	88 (28.4)	22 (7.1)	87 (28.1)		22 (8.8)	34 (13.7)	193 (77.5)	
Anatomical location									
Upper lip	4 (16.7)	9 (37.5)	0 (0.0)	11 (45.8)	0.140	0 (0.0)	2 (8.7)	21 (91.3)	0.389
Lower lip	327 (31.8)	286 (27.8)	77 (7.5)	338 (32.9)		59 (7.1)	84 (10.2)	684 (82.7)	
Manifestation type									
Primary	226 (30.7)	201 (27.3)	55 (7.5)	253 (34.4)	0.055	44 (6.4)	68 (9.9)	573 (83.7)	0.410
Recurrent	41 (38.0)	29 (26.8)	13 (12.0)	25 (23.1)		1 (2.4)	6 (14.3)	35 (83.3)	
Habits									
Tobacco smoking									
Yes	33 (41.2)	23 (28.7)	3 (3.7)	21 (26.2)		8 (6.6)	10 (8.3)	103 (85.1)	
No	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	**0.032***	0 (0.0)	0 (0.0)	24 (100.0)	**0.004***
Ex-smoker	7 (30.4)	12 (52.2)	1 (4.3)	3 (13.0)		3 (8.8)	9 (26.5)	22 (64.7)	
Alcohol consumption									
Yes	15 (45.4)	7 (21.2)	3 (9.1)	8 (24.2)		5 (10.2)	6 (12.2)	38 (77.6)	
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.695	0 (0.0)	0 (0.0)	23 (100.0)	**0.020***
Ex-consumer	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)		1 (4.0)	7 (28.0)	17 (68.0)	
Chronic solar exposure									
Yes	21 (28.0)	10 (13.3)	6 (8.0)	38 (50.7)	0.193	2 (2.2)	1 (1.1)	88 (96.7)	0.737
No	2 (28.6)	3 (42.9)	0 (0.0)	2 (28.6)		0 (0.0)	0 (0.0)	18 (100.0)	
Previous AC									
Yes	-	-	-	-		3 (4.2)	1 (1.4)	68 (94.4)	**0.018***
No	-	-	-	-		56 (7.2)	85 (10.9)	637 (81.9)	

[a]Chi-square test.

***P-value statistically significant**

.

Table 4. Association of age and evolution time with dysplasia grade and symptomatology for actinic cheilitis (AC) and association of age and evolution time with invasion pattern and symptomatology for lip squamous cell carcinoma (LSCC)

	AC				LSCC			
	Age (years)	***P*-value**	**Evolution time (months)**	***P*-value**	**Age (years)**	***P*-value[a]**	**Evolution time (months)**	***P*-value**
	Mean (SD)		**Mean (SD)**		**Mean (SD)**		**Mean (SD)**	
Dysplasia								
Mild	56.7 (13.3)	0.435*	45.5 (69.8)	**0.026***	-	-	-	-
Moderate	55.0 (14.4)		35.1 (65.3)		-		-	
Severe	55.3 (14.3)		17.5 (18.4)		-		-	
Absent	56.5 (14.0)		29.2 (51.4)		-		-	
Symptomatology								
Yes	31.6 (60.9)	0.369**			15.2 (19.1)	0.335**		
No	37.5 (69.5)				21.9 (39.6)			
Invasion								
In situ	-	-	-	-	59.1 (11.4)	0.707*	26.1 (32.6)	**0.002***
Superficially invasive	-		-		60.3 (15.0)		46.2 (114.8)	
Invasive	-		-		60.7 (14.7)		20.2 (33.6)	

*ANOVA test; ** t-Student test.

Bold represents *P*-value statistically significant.

Figure 1.

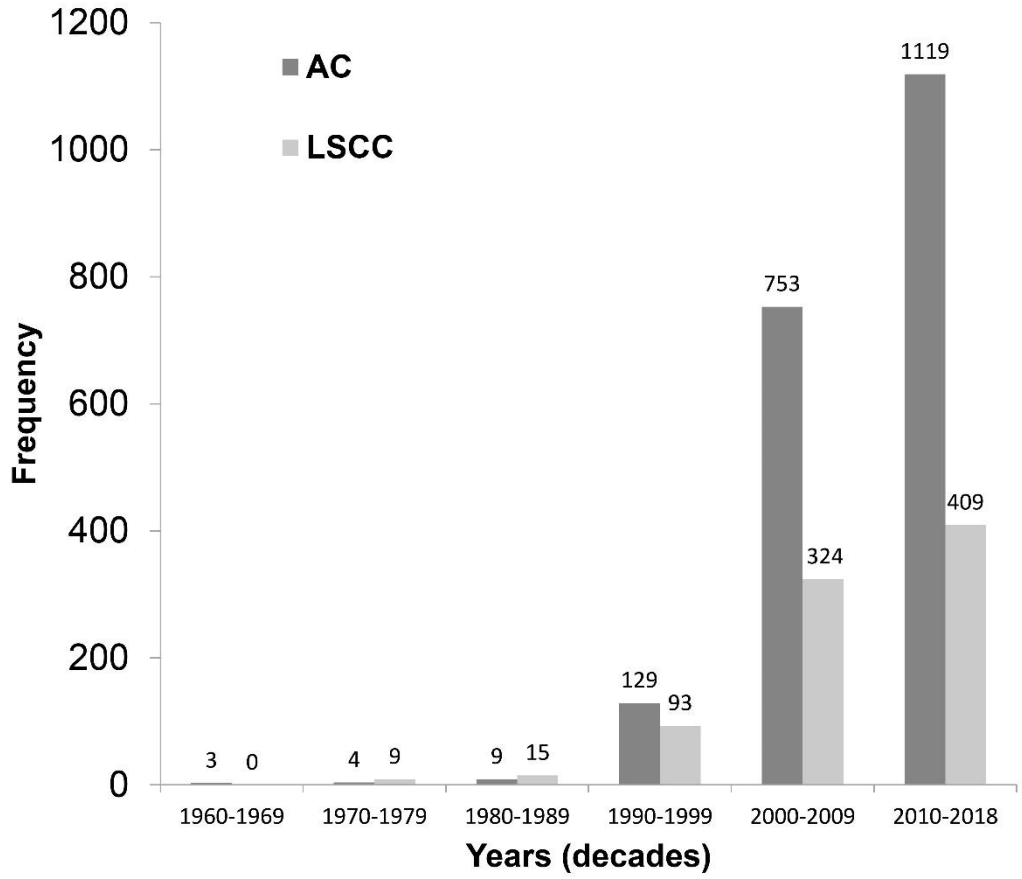

1200
1000
800
600
400
200
0
Frequency
AC
LSCC
3
0
4
9
9
15
129
93
753
324
1119
409
1960-1969
1970-1979
1980-1989
1990-1999
2000-2009
2010-2018
Years (decades)

Figure 2. Clinical features of actinic cheilitis.

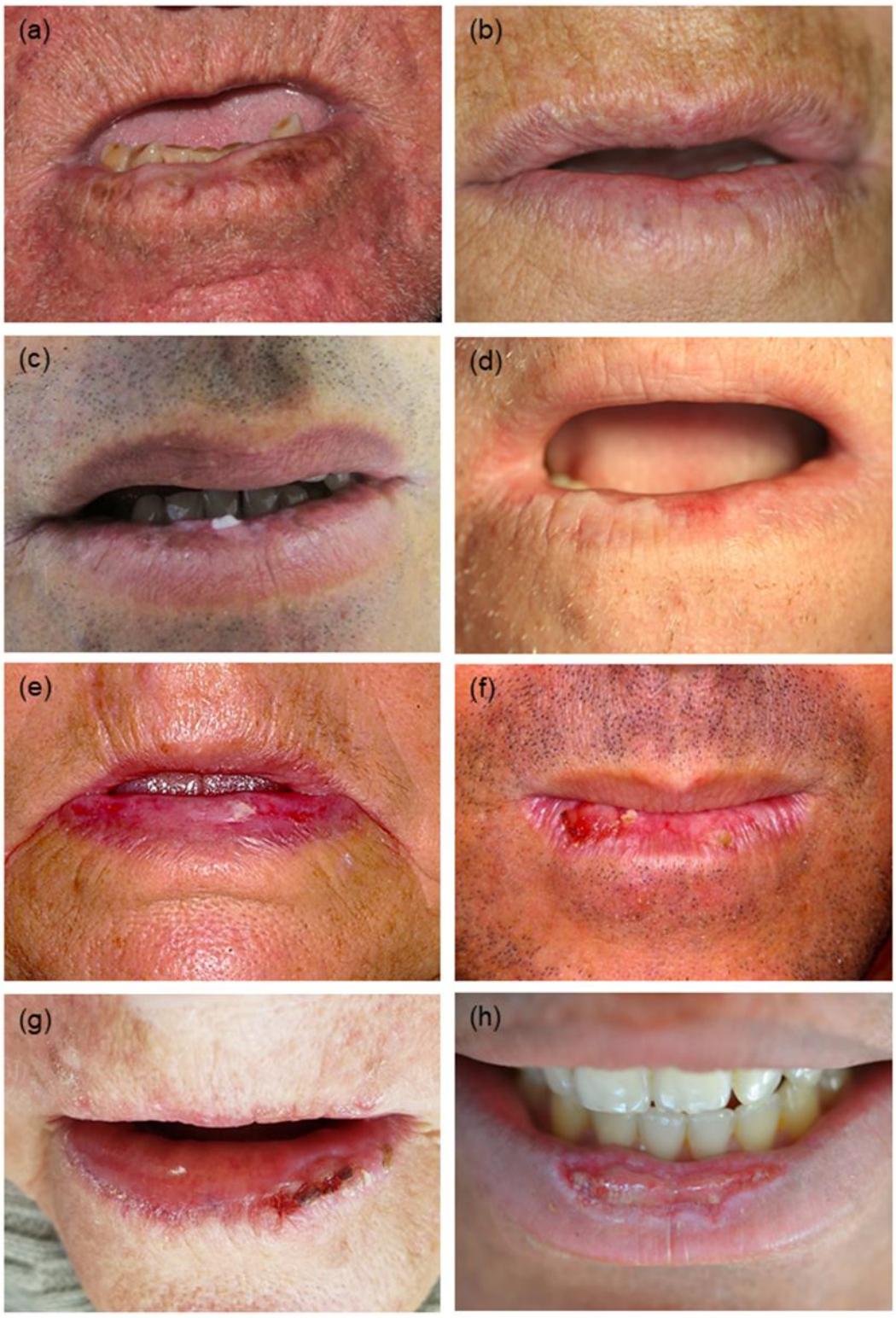


Figure 3. Clinical features of lip squamous cell carcinoma cases.

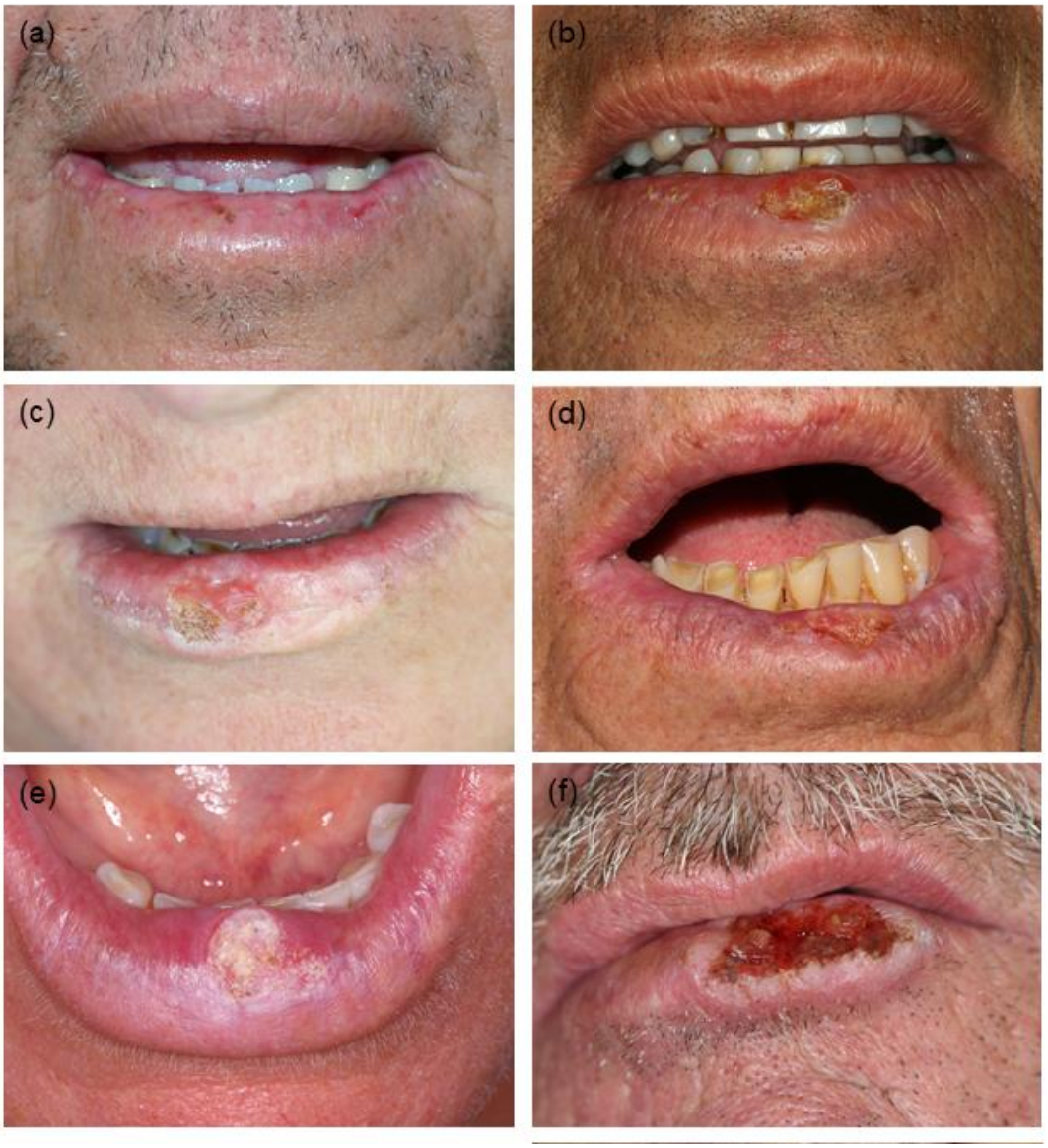
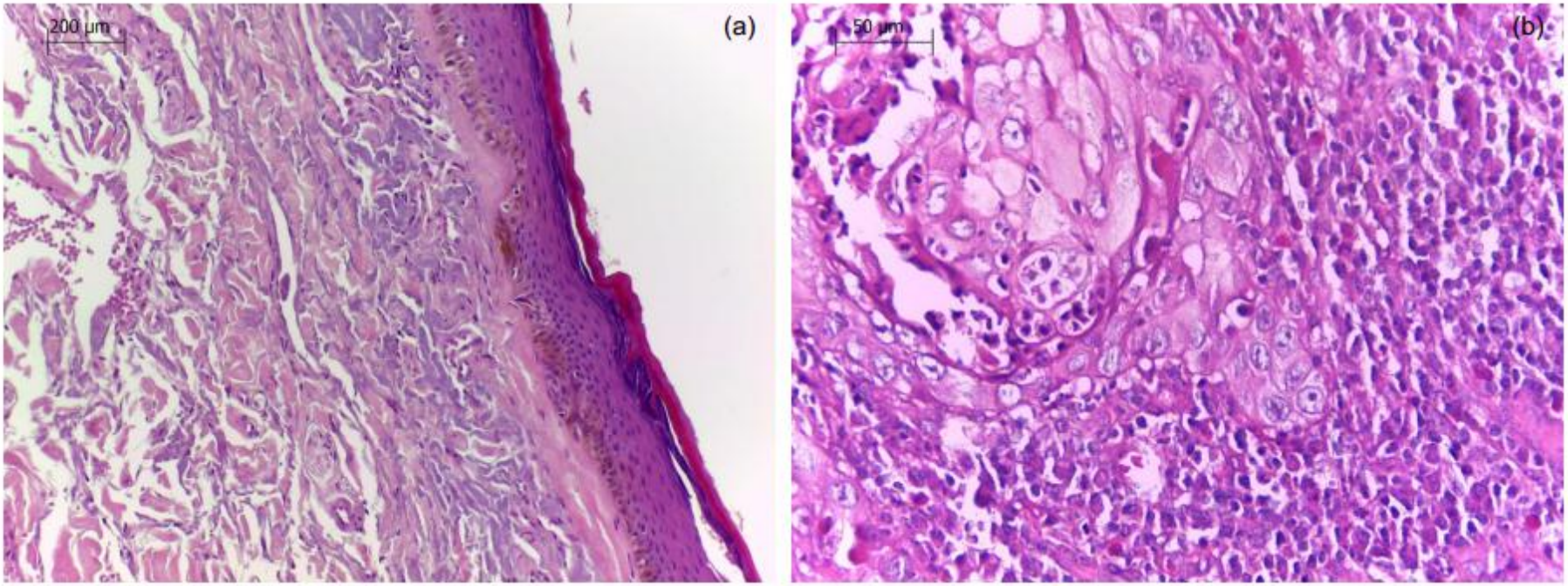


Figure 4. Histopathological features of actinic cheilitis and lip squamous cell carcinoma cases, respectively.



4 CONSIDERAÇÕES FINAIS

Neste estudo multicêntrico brasileiro, 2.017 casos de QA e 850 casos de CCEL foram analisados. A QA e o CCEL são lesões relativamente incomuns quando comparadas a outras lesões biopsiadas, representando 1,0 e 0,4% dos casos em toda a amostra de lesões orais e maxilofaciais diagnosticadas, respectivamente. Observou-se um aumento do número de casos dessas lesões e um diagnóstico mais tardio, especialmente da QA, principalmente a partir dos anos 2000.

A frequência e as características clinicopatológicas tanto da QA quanto do CCEL foram semelhantes às descritas em geral no mundo. As lesões exibiram predileção por indivíduos do sexo masculino, brancos, na sétima década de vida e na maioria dos casos, trataram-se de lesões assintomáticas com acometimento predominante no lábio inferior. Os hábitos, principalmente o fumo, estão associados ao grau de displasia e, mais ainda, ao padrão de invasão. Lesões com maior grau de displasia e padrão de invasão apresentaram menor tempo de evolução.

Este é o maior estudo multicêntrico de QA e CCEL do Brasil e essa caracterização em um país tão grande e com tantas diferenças regionais fortalece evidências e fornece dados epidemiológicos robustos e representativos para clínicos, dermatologistas, estomatologistas e oncologistas e para o desenvolvimento de políticas públicas na prevenção dessas lesões na população brasileira.

REFERÊNCIAS

1. MARTINS-FILHO, P. R. S.; DA SILVA L. C. F.; PIVA, M. R. The prevalence of actinic cheilitis in farmers in a semi-arid northeastern region of Brazil**. Int J Dermatol**, v. 50, n. 9, p. 1109–1114, Set. 2011.

2. MARKOPOULOS, A.; ALBANIDOU-FARMAKI, E.; KAYAVIS, I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. **Oral Dis**, v. 10, n. 4, p. 212-216, Jul. 2004.

3. WARNAKULASURIYA, S.; JOHNSON, N. W.; VAN DER WAAL, I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. **J Oral Pathol Med**, v. 36, n. 10, p. 575-580, Nov. 2007.

4. RODRÍGUEZ-BLANCO, I. *et al*. Actinic Cheilitis Prevalence and Risk Factors: A Cross-sectional, Multicentre Study in a Population Aged 45 Years and Over in North-west Spain. **Acta Derm Venereol**, v. 98, n. 10, p. 970-974, Nov. 2018.

5. CAVALCANTE, A. S.; ANBINDER, A. L.; CARVALHO, Y. R. Actinic cheilitis: clinical and histological features. **J Oral Maxillofac Surg**, v. 66, n. 3, p. 498-503, Mar. 2008.

6. ROSSOE, E. W. T. *et al*. Queilite actínica: avaliação comparativa estética e funcional entre as vermelhectomias clássica e em W-plastia. **An Bras Dermatol**, v. 86, n.1, p. 65-73, Fev. 2011.

7. JUNQUEIRA, J. L. *et al*. Actinic cheilitis among agricultural workers in Campinas, Brazil. **Community Dent Health**, v. 28, n. 1, p. 60-63, Mar. 2011.

8. DE SANTANA SARMENTO, D. J. *et al*. Actinic cheilitis: clinicopathologic profile and association with degree of dysplasia. **Int J Dermatol**, v. 53, n. 4, p. 466-472, Abr. 2014.

9. KUJAN, O. *et al*. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. **Oral Oncol**, v. 42, n. 10, p. 987–993, Nov. 2006.

10. KUJAN, O. *et al*. Why oral histopathology suffers inter-observer variability on grading oral epithelial dysplasia: An attempt to understand the sources of variation. **Oral Oncol**. v.43, n.3, p. 224- 231, Mar. 2007.

11. WARNAKULASURIYA S. Histological grading of oral epithelial dysplasia: revisited. **J Pathol**. v. 194, n. 3, p. 294-297, Jul. 2001.

12. EL-NAGGAR, A. K.; CHAN, J. K. C.; GRANDIS, J. R.; TAKATA, T.; SLOOTWEG, P. J. **World Health Organization Classification of Head and Neck Tumours**. 4th. ed. Lyon: IARC Press, 2017.

13. FERREIRA, A. M. *et al*. Prevalence and factors associated with oral potentially malignant disorders in Brazil's rural workers. **Oral Dis**. v. 22, n. 6, p. 536-542, Set. 2016.

14. SILVEIRA, É. J. *et al*. Potentially malignant oral lesions: clinical and morphological analysis of 205 cases. **J Bras Patol Med Lab**, v. 45, n. 3, p. 233-8, Jun. 2009.

15. DE ROSA, I. *et al*. Potentially malignant and malignant lesions of the lip. Role of silver staining nucleolar organizer regions, proliferation cell nuclear antigen, p53, and c-myc in differentiation and prognosis. **J Oral Pathol Med**. v. 28, n. 6, p. 252-258, Jul. 1999.

16. DANCYGER, A. *et al*. Malignant transformation of actinic cheilitis: A systematic review of observational studies. **J Investig Clin Dent**. v.9, n.4, p. e12343, Nov. 2018.

17. MOORE, S. R. *et al*. The epidemiology of lip cancer: A review of global incidence and aetiology. **Oral Dis**. v. 5, n. 3, p. 185-195, Jul. 1999.

18. BIASOLI, É. R. *et al*. Lip Cancer: A Clinicopathological Study and Treatment Outcomes in a 25-Year Experience. **J Oral Maxillofac Surg**. v. 74, n. 7, p. 1360-1367, Jul. 2016.

19. MIRANDA, A. M. *et al*. Prevalence of actinic cheilitis in a population of agricultural sugarcane workers. **Acta Odontol Latinoam**. v. 25, n. 2, p. 201-207, Dez. 2012.

20. LOPES, M. L. *et al*. Clinicopathological profile and management of 161 cases of actinic cheilitis. **An Bras Dermatol**. v. 90, n. 4, p. 505-512, Ago. 2015.

21. DE VISSCHER, J. G. *et al*. Epidemiology of cancer of the lip in The Netherlands. **Oral Oncol**. v. 34, n. 5, p. 421-426, Set. 1998.

22. MELLO, F. W. *et al*. Actinic cheilitis and lip squamous cell carcinoma: Literature review and new data from Brazil. **J Clin Exp Dent**. v. 11, n. 1, p. e62-e69, Jan. 2019.

23. PEREA-MILLA LÓPEZ, E. *et al*. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case-control study in southern Spain. **Br J Cancer**. v. 88, n. 11, p. 1702-1707, Jun. 2003.

24. VAN LEEUWEN, M. T. *et al*. Immunosuppression and other risk factors for lip cancer after kidney transplantation. **Cancer Epidemiol Biomarkers Prev**. v. 18, n. 2, p. 561-569, Fev. 2009.

25. CALDEIRA, P. C. *et al*. Thioredoxin and metallothionein: Homeostasis-related proteins in lip carcinogenesis. **Arch Oral Biol**. v. 77, p. 75-81, Mai. 2017.

26. BELSEY, A. Patients, doctors and experimentation: doubts about the Declaration of Helsinki. **J Med Ethics**. v. 4, n. 4, p.182-185, 1978.

ANEXO A – Aprovação do comitê de ética em pesquisa

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Queilite actínica: um estudo multicêntrico
Pesquisador: Ricardo Alves de Mesquita
Área Temática:
Versão: 1
CAAE: 98594918.0.1001.5149
Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.936.807

Apresentação do Projeto:
A queilite actínica é um processo inflamatório crônico que normalmente atinge a região de vermelhão do lábio inferior de indivíduos expostos regularmente e excessivamente à luz solar sem qualquer tipo de proteção. É considerada uma desordem potencialmente maligna que pode evoluir para um carcinoma de células escamosas invasivo. Os objetivos do trabalho são determinar a frequência de queilite actínica em diferentes regiões do Brasil, estabelecer o perfil demográfico dos pacientes com esta lesão, fazer uma análise temporal do número de casos por região e verificar a associação entre a frequência da queilite actínica e a incidência solar nos respectivos estados estudados. As amostras serão obtidas por meio de fichas clínicas e laudos histopatológicos do arquivo do Serviço de Patologia Oral e Maxilofacial de dez centros de referência no Brasil. Dados de sexo, idade, cor da pele, ocupação, hábitos, tempo da lesão, tipo de manifestação e diagnóstico histopatológico das lesões serão coletados. Para caracterizar os casos será feita análise estatística descritiva utilizando o software SPSS (versão 17.0, Chicago, IL, USA) e, para verificar a existência de associação entre a frequência da lesão e a incidência solar nos estados, será utilizado teste de normalidade e, posteriormente, o Teste t-student ou Mann-Whitney dependendo da distribuição da amostra. Espera-se encontrar diferença na distribuição de queilite actínica nas diferentes regiões do país e associação significativa entre a incidência solar no estado e a frequência da lesão.

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Bairro: Unidade Administrativa II **CEP:** 31.270-901
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Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

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Objetivo da Pesquisa:

Hipótese:

Encontrar diferença na distribuição da QA nas diferentes regiões do país, bem como associação significativa entre a incidência solar no estado e a frequência da lesão, baseada no princípio de que quanto mais próximo aos polos maior a variabilidade do fotoperíodo.

Objetivo Primário:

Determinar a prevalência de QA em diferentes regiões do Brasil.

Objetivo Secundário:

- Descrever o perfil demográfico de pacientes com diagnóstico de queilite actínica (sexo, idade, cor da pele, ocupação e hábitos);
- Avaliar o tempo de desenvolvimento da lesão e o tipo de manifestação (primária ou recidivante);
- Analisar temporalmente o número de casos de QA em cada centro;
- Verificar a associação entre a incidência solar nas regiões participantes do estudo (Norte, Nordeste, Sul, Sudeste e Centro-Oeste) e a frequência da lesão em cada uma delas;
- Caracterizar histopatologicamente os casos de queilite actínica;
- Caracterizar os aspectos clínicos dos casos diagnosticados histologicamente como carcinoma de células escamosas cujo diagnóstico clínico foi de queilite actínica.

Avaliação dos Riscos e Benefícios:

De acordo com os autores:

Riscos:

No caso de coleta de dados através de fichas de arquivos, considera-se o risco de identificação do indivíduo. Entretanto, nós nos responsabilizamos no anonimato desses indivíduos em todo momento da pesquisa.

Benefícios:

Contribuir para a saúde pública no sentido de gerar conhecimento sobre a distribuição da doença no país e suas características possibilitando assim o foco de políticas preventivas em locais onde a prevalência e/ou incidência solar forem elevadas.

Comentários e Considerações sobre a Pesquisa:

Pesquisa relevante para a Odontologia, em especial para as áreas de Estomatologia, Patologia

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Bucal e Cirurgia Bucomaxilofacial. Trata-se da dissetação de Mestrado da pós-graduanda Leni Verônica de Oliveira Silva, sob orientação do Prof. Dr. Ricardo Alves Mesquita. Término previsto para 12/07/2019.
A proposta é de um estudo multicêntrico, com 10 centros participantes, abrangendo todas as regiões do Brasil.

Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados os seguintes documentos:

- Informações Básicas do Projeto;
- Parecer do Programa de Pós-graduação em Odontologia, da Faculdade de Odontologia da UFMG, aprovado pela Coordenação do Colegiado do Programa de Pós-graduação em Odontologia e aprovado ad referendum pelo chefe do departamento;
- Projeto Detalhado / Brochura Investigador;
- Justificativa de dispensa de TCLE;
- Folha de Rosto;
- Orçamento (financiamento);
- Cronograma de execução da pesquisa;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa do Hospital das Clínicas de Porto Alegre, da Universidade Federal do Rio Grande do Sul - UFRGS;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa da Faculdade de Odontologia da Universidade Federal de Minas Gerais - UFMG;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa da Faculdade de Odontologia da Universidade de Pernambuco - UPE;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa da Faculdade de Odontologia da Universidade de São Paulo - USP;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa do Departamento de Odontologia da Universidade Federal do Rio Grande do Norte - UFRN;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa da Faculdade de Odontologia da Universidade Federal do Rio de Janeiro - UFRJ;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa da Faculdade de Odontologia da Universidade Federal de Pelotas - UFPel;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa do Laboratório de Patologia Bucal do Hospital Universitário João de Barros Barreto, da Universidade Federal do Pará - UFPA;

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- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa da Faculdade de Odontologia da Universidade Federal de Goiás - UFG;
- Autorização do responsável pelo setor para obtenção dos dados a serem utilizados na pesquisa do Departamento de Odontologia da Universidade Estadual da Paraíba - UEPB.

Foi solicitada dispensa do TCLE com a seguinte justificativa:

"O estudo é retrospectivo com uso de banco de dados secundário de Serviços de Patologia Oral e Maxilofacial. Todos estes serviços apresentarão o termo de Aceitação de Participação do projeto. Ademais, declaramos conhecer e cumprir as Resoluções Éticas Brasileiras, em especial a Resolução CNS 466/12. As Instituições participantes nesse estudo estão cientes de suas co-responsabilidades como Instituição co-participante do presente projeto de pesquisa e de seu compromisso no resguardo da segurança e bem-estar dos sujeitos da pesquisa nela analisados. Por fim, asseguramos preservar a identidade das fichas de biópsias, resguardando o nome dos indivíduos e fotografias."

Recomendações:

Recomenda-se,s.m.j., a aprovação do Projeto de Pesquisa "Queilite actínica: um estudo multicêntricoQueilite actínica: um estudo multicêntrico" do Professor Responsável Ricardo Alves de Mesquita.

Conclusões ou Pendências e Lista de Inadequações:

Projeto de Pesquisa Aprovado.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o CEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1167452.pdf	17/09/2018 10:55:54		Aceito

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Continuação do Parecer: 2.930.807

Outros	Parecer_consubstanciado.pdf	06/09/2018 17:10:55	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UFRGS.pdf	06/09/2018 17:08:31	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Projeto Detalhado / Brochura Investigador	2018_Projeto_Mestrado_COEP.pdf	06/09/2018 17:06:48	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UFMG.pdf	23/07/2018 14:56:06	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	JUSTIFICATIVA_NAO_TCLE.pdf	29/06/2018 15:46:58	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Folha de Rosto	FOLHA_DE_ROSTO_LENI.pdf	29/06/2018 15:30:06	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Orçamento	FINANCIAMENTO.pdf	26/06/2018 19:33:07	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UPE.pdf	26/06/2018 17:52:48	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	USP.pdf	26/06/2018 17:46:37	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UFRN.pdf	26/06/2018 17:45:55	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UFRJ.pdf	26/06/2018 17:45:38	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UFPel.pdf	26/06/2018 17:45:23	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UFPA.pdf	26/06/2018 17:45:07	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UFG.pdf	26/06/2018 17:44:33	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Outros	UEPB.pdf	26/06/2018 17:44:14	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito
Cronograma	CRONOGRAMA.pdf	26/06/2018 17:28:21	LENI VERÔNICA DE OLIVEIRA SILVA	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

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BELO HORIZONTE, 04 de Outubro de 2018

Assinado por:
Eliane Cristina de Freitas Rocha
(Coordenador(a))

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ANEXO B – Informações e normas da revista onde o artigo foi submetido

Histopathology
ISSN on-line: 1365-2559
Qualis: A1
Fator de Impacto: 3.267

Normas da revista

Every manuscript should have:

A concise cover letter

A Microsoft Word (or equivalent) file (NOT A PDF) that is presented in English, in a double spaced format using a standard font (e.g. Arial, Helvetica, Times Roman etc 12 point) and has page numbers

A title page (or pages) containing:
• A succinct and clear title that accurately describes the work contained within the manuscript.
• A short running title (up to 50 characters including spaces)
• List of authors (using given and family name, but not degrees)
• Full affiliations of all authors and contact details of the corresponding author(s)
• A conflict of interest statement
• A word count (from beginning of Introduction to end of Discussion)

The next page should have:
• An Abstract (structured and no more than 250 words)
• Keywords (3 to 8) preferably chosen from the medical subject headings (MeSH) in Index Medicus.

The manuscript should contain the following:
• Introduction
• Materials and methods
• Results
• Discussion
• Acknowledgements which should include a statement defining funding sources
• List of abbreviations (optional)
• List of online Supporting Information (if any)
• Reference list in the correct format (see below)
• Table(s)
• Figure legends (concise and not repeating material in the Results section)

As separate files:
• Figures (at the appropriate size and resolution [http://authorservices.wiley.com/electronicartworkguidelines.pdf])
• Supporting Information files (if any)
• Additional Files for Review but NOT for publication
• Patient Consent Form (where relevant)

Submission Checklist
The manuscript must be submitted via the online submission system (and not by mail or email), which is located at: **http://mc.manuscriptcentral.com/histop**

• Your Histopathology Manuscript Central username and password (unless you are a new user)

• All manuscript, figure and Supporting Information files finalised and ready to upload
• Permission to reproduce any previously published material scanned and ready to upload
• Full correct names and E-mail addresses of all of your co-authors.
• The names and full contact details of up to three suggested referees
• Additional files for review but not for publication may be provided

Review Process

An initial assessment will be made by the Editor-in-Chief (or one of three Regional Editors) following submission of your manuscript. This process considers whether the submitted work falls within the scope of Histopathology (see above) and is of initial interest and/or scientific worth to merit possible publication. At this point a proportion of manuscripts will be returned to the authors.
Manuscripts that enter the review process are assigned sequentially to a relevant Associate Editor who invites reviewers (normally two external reviews are sought). The reviewers' evaluations and Associate Editor's comments are submitted to the Editor-in-Chief (or the relevant Regional Editor) to inform a final decision. We aim to convey a decision within four weeks of the receipt of the manuscript.
The Editor-in-Chief or Regional Editor will advise authors whether a manuscript is accepted, requires revision, or is rejected. Revisions are expected to be returned within four weeks of decision. Manuscripts not revised within this time are subject to withdrawal from consideration for publication unless there are extenuating circumstances.
Please note that some manuscripts will have to be rejected on the grounds of priority, interest, journal balance and available space. Invitation to submit a revised manuscript does not imply that acceptance will automatically follow.
Authors may provide the Editor-in-Chief /Regional Editors with the names, addresses and email addresses of up to three suitably qualified individuals of international standing who would be competent to referee the paper, although the Editorial team will not be bound by any such nomination. Likewise, authors may advise of any individual who for any reason, such as potential conflict of interest, might be inappropriate to act as a referee, again without binding the Editor-in-Chief.
The decision of the Editor-in-Chief is final. If, however, authors dispute a decision and can document good reasons why a manuscript should be reconsidered, a rebuttal process exists. In the first place, authors should write to the Editor-in-Chief outlining their case.

Detailed guidance on the preparation of manuscripts
Cover letter
Submission of a manuscript will be held to imply that it contains original unpublished work and is not being submitted for publication elsewhere at the same time. This should be confirmed in the covering letter. The corresponding author must confirm that all authors have agreed with the submission in its present (and subsequent) forms. The authors should also indicate in their covering letter: the aim of the study; the significant and novel findings and where relevant how the findings could influence clinical practice.

General points
The manuscript should be prepared using a word processing package, using a standard font, double spaced with margins of at least 2 cm and have page numbers. Do not use line numbering. The manuscript should be in English using consistent and preferably UK spelling.

Manuscript title
The title of the paper should be short and must summarise the content of the article. It should be presented in a way that catches the attention of readers. It must however be accurate and unambiguous and should focus on the message of the paper.

Short running title
This should be concise (maximum of 50 characters including spaces) and reflect the main title and content of the manuscript.

List of contributors
All those designated as authors should qualify for authorship and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One author (deemed to be the Corresponding Author) should take responsibility for the integrity of the work as a whole, from inception to published article. Joint first authorship is permitted but this is normally restricted to two contributors unless there are exceptional circumstances.
Authorship credit should be based only on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published. Provision of funding, collection of data or general supervision of the research group alone does not justify authorship. All others who contributed to the work who are not authors should be named in an Acknowledgements section.
If you are submitting a revised article and the authors have changed from the original submission, for example: if additional authors are added [or removed] then agreement of all authors is mandatory with justification and explanation required within the covering letter, submitted via the ScholarOne system.

Full affiliations of all authors
This should include the name of the department(s) and institution(s) to which the work should be attributed, and contact details of the corresponding author i.e. the full postal address, phone number and email address.

Conflict of interest statement
Authors are responsible for disclosing all financial and personal relationships between themselves and others that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should describe the role of the study sponsor(s), if any, in study design, in the collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the report for publication.
A conflict of interest statement must be included in the manuscript (on the title page) that details any conflicts that exist for each author, or declares the absence of conflict for each author; this will be incorporated into the text of any accepted article.

We provide here details of some example situations or arrangements that the Editors of Histopathology would deem to result in a conflict of interest:
• Private or corporate funding of any part of the study, or donation or loan of supplies or equipment. In such cases role of the study sponsor or donor(s), if any, in the study design; data collection, analysis or interpretation; or writing of the report must be made clear.
• For each author (or their immediate family members):
• Employment by a company that produces a material or equipment used in the study.
• The receipt of financial or other compensation (such as cash, travel/accommodation costs, royalties, fees, stock or stock options) for work; advising or consulting; expert testimony or advocacy/public speaking from companies, organizations, institutions, and individuals.
• The ownership of financial holdings or considerations, such as stocks or bonds in a company that could be construed as gaining from the conclusions of the study.
• The holding of a patent on a method or equipment used in the study, or that employs a principle validated by the study.
• The presence of personal, professional, political, institutional, religious, or other associations that could have a bearing upon the stance taken in the submitted work.

Full details of the conflicts of interest of our Editor-in-Chief, Regional Editors and Associate Editors are held on record at the journal offices.
We ask our Editors to identify any manuscripts for which there is a real or perceived conflict of interest; they would not participate in the review process in such a situation. Similarly we ask reviewers to similarly declare any conflict of interest and decline invitations to review if this exists. With regard to conflict of interest we are guided by the principles laid down by the Committee on

Publication Ethics (http://www.publicationethics.org.uk), the International Committee of Medical Journal Editors (Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication Updated October 2008 **http://www.icmje.org/#conflicts**) and the World Association of Medical Editors (WAME Editorial Policy and Publication Ethics Committees Conflict of Interest in Peer-Reviewed Medical Journals Posted March 27, 2009. http://www.wame.org/conflict-of-interest-in-peer-reviewed-medical-journals).

Word count (from beginning of Introduction to end of Discussion)
The length of the manuscript should normally be no more than 2500 words. The use of online Supporting Information as a route for presenting additional material is available. When using the device of Supporting Information for additional text or data, authors should remember that the main manuscript must contain sufficient information to make the work intelligible without resort to the Supporting Information. For example, it is not acceptable to shorten a manuscript by placing all of the Materials and Methods in Supporting Information. However it is acceptable to place some aspects of experimental detail in Supporting Information.

Abstract (Structured and no more than 250 words)
After the title page(s) the next page should carry an abstract of no more than 250 words which includes subsections: Aims; Methods and results; Conclusions. The abstract should be concise and clear. It should emphasise new and important aspects of the study. It should be understandable without reference to the rest of the paper and should contain no citation to references in the reference list. Non-standard abbreviations should be avoided. Advice on how to optimise your abstract for search engines can be found here.

Keywords
Below the abstract, authors should provide and identify as such 3 to 8 keywords or short phrases to assist indexing the article and that may be published with the abstract. MESH headings are a useful guide for authors in considering keywords.

Manuscript structure: general aspects
As noted above full articles should usually be no more than 2500 words from the beginning of the Introduction to the end of the Discussion, which is approximately nine journal pages, when tables, figures and references are also included.
Review articles may exceed these limits by arrangement with the Editor-in-Chief. Please remember that succinct articles are likely to make a greater impact on readers than long ones and are likely to proceed more rapidly though the editorial process post-acceptance..
The text of research articles should be divided into sections with the headings: Abstract, Introduction, Methods, Results and Discussion. Some articles may need subheadings within sections (especially the Results and Discussion sections) to clarify their content. Such sections however should not be numbered.
Other types of articles, such as reviews and short reports, still need a title and abstract and should adhere as closely as possible to these guidelines. This is not required in items of correspondence.
Review articles and commentaries/editorials have greater flexibility than standard original articles although a concise clear style is essential. Such articles are usually by invitation although the editorial team is happy to receive suggestions and outlines of possible material of this kind. All such material, whether invited or not, will normally undergo peer review.
Editorials usually take the form of a brief (typically 2 to 3 journal pages) review that places a paper (or group of papers) published in the issue into a broader context. They should be focussed and pithy. They should be accessible to a broader audience than the primary papers might be. Diagrams are often useful to illustrate concepts and ideas.

The nature of a review article is self-explanatory. These might be of variable length from short items (mini-review) through to very detailed, fully referenced contributions.
Items of correspondence: Case reports, comments on previously published papers, items of topical interest, and brief original communications will be considered under this heading. The letter should not be divided into sections. No abstract is required. The length, including references, should be between 600 and 800 words. You should include no more than six

references. Submit no more than two black and white or coloured illustrations; each should not exceed one column width.
Short reports: The Journal will consider brief original reports; the length should not exceed 1500 words. It should still include a structured abstract of 250 words. It should not contain more than two figures or tables, or one of each.
Lesson of the Month: Articles submitted for “Lesson of the Month” should be succinct with a punchy title and provide novel information to the reader. Such articles might include a description of a case (or cases) that raises interesting diagnostic issues from which an important lesson is learnt. This may include cases where errors have been made. Examples could include cases where there is a differential diagnosis and a particular immunostain is misleading or the description of a previously unreported iatrogenic artefact. No abstract is required. The length, including references, should be between 600 and 800 words. You should include no more than six references. Submit no more than two black and white or coloured illustrations; each should not exceed one column width.

Manuscript structure: specific guidance

Introduction
Authors should state the purpose of the article and summarise the rationale for the study or observation, providing relevant background. The length of the Introduction is not specified but it should be in proportion to the rest of the manuscript and sufficiently comprehensive to allow a non specialist to understand the setting of the work. Give only strictly pertinent references and avoid the inclusion of data or conclusions from the work being reported. The aims of the study and hypothesis being tested should be stated clearly and objectively.

Materials and methods
• Ethical issues:

• A statement describing explicitly the ethical background to the studies being reported should be included in all manuscripts in the Materials and Methods section. Ethics committee or institutional review board approval should be clearly stated and the relevant reference numbers and dates must be given. Do not use patients’ names, initials or hospital numbers, especially in illustrative material.
• The Journal recognises that the requirements and legislation pertaining to all aspects of ethical review may vary between different jurisdictions. If there are any legitimate concerns raised by reviewers or editors about any aspect of the ethical issues of the study that cannot be satisfactorily resolved, the Editor-in-Chief reserves the right to decline to publish the manuscript. The current ethical policies of Histopathology can be found at**http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2559/homepage/ethical_policy_of_histopathology.htm** .
• As a member of the Committee on Publication Ethics (COPE), adherence to these submission criteria is considered essential for publication in Histopathology. If, at any stage in the submission and review process or even after publication, a manuscript or authors are found to have disregarded these criteria, it is the duty of the Editor-in-Chief to report this to COPE. COPE may recommend that action may be taken, including but not exclusive to, informing the authors’ professional regulatory body and/or institution of such a dereliction. The website for COPE may be accessed at:**http://www.publicationethics.org.uk**
• If concerns are raised regarding potential misconduct, such as plagiarism, redundant publication, or fabrication or manipulation of data, authors should be aware that the Journal will follow the COPE guidelines in dealing with the case, which, if the Journal is not satisfied with the authors’ explanation, can lead to the withdrawal of a manuscript from peer-review, or the publication of a retraction, and also to the Journal informing the authors’ professional regulatory body and/or institution of the details of the case.

Patient consent: Images of, or Information about, Identifiable Individuals: It is the author¹s responsibility to obtain consent from patients and other individuals for use of information, images, audio files, interview transcripts, and video clips from which they may be identified. To ensure we have the rights we require please provide a signed consent/release form in all instances.
- If the person is a minor, consent must be obtained from the child¹s parents or guardians.

- If the person is deceased, we consider it essential and ethical that you obtain consent for use from the next of kin. If this is impractical you need to balance the need to use the image against the risk of causing offence. In all cases ensure you obscure the identity of the deceased.
- If using older material, or for material obtained in the field, for which signed release forms are, for practical purposes, unobtainable, you will need to confirm in writing that the material in question was obtained with the person¹s understanding that it might be published.

• General aspects of Materials and Methods:
• Describe the methods, reagents and equipment (give the manufacturer's name and address in parentheses) and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods.
• Studies on biomarkers and/ or prognostic and predictive factors must describe the patient selection criteria and provide a detailed breakdown of the cohort(s) included in the study.
• Important information that is not essential for the understanding of the manuscript may appear as Supporting Information online. Examples of this might include PCR primer sequences and extraneous experimental detail. As a guide, information required to understand what was done and how, should be in the manuscript.
• Reliable studies of clinical samples require high quality samples and we anticipate that authors will document BRISQ Tier one variables See: Simeon-Dubach D, Burt AD, Hall PA. Quality really matters: the need to improve specimen quality in biomedical research. Histopathology. 2012;61(6):1003-5

Histopathology is interested in personalized medicine research describing biomarkers of therapeutic outcome or response. Predictive biomarker studies that estimate response or survival in advance of therapy or pharmacodynamic biomarker studies that are associated with target modulation are of particular interest. Highest priority will be given to those articles that are likely to have direct clinical applications and are definitive based on size of cohort, methodological approach, statistical analysis, multivariate analysis, reproducibility, and patient follow-up. Personalized medicine biomarker studies should have the following characteristics:
• They are definitive in size and statistical power. Prospective studies or prospective-retrospective studies will receive priority. Retrospective studies will be considered, but they should include verification using an independent cohort.
• They describe a unique cohort with results that directly impact clinical practice. (For rare cancer types, it is recognized that small cohorts will be analyzed.)
• They adhere to the REMARK criteria as listed in their guidelines (**http://jnci.oxfordjournals.org/content/97/16/1180/T1.expansion.html**).
• They contain thorough specimen collection data, assay validation, and statistical rigor.
• They are based on (or include) mechanistic data.
• Statistics and bioinformatics
• You must describe statistical and bioinformatic approaches for both data processing and analysis with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of error or uncertainty (such as standard error or confidence intervals). Sample size should always be indicated. References for the design of the study and statistical methods should usually be to standard works (with pages stated) but citation to the papers in which the designs or methods were originally reported may sometimes be appropriate.
• Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Where possible use graphs as an alternative to tables.
• The checklist for statisticians published by the BMJ is a valuable resource (see:**http://resources.bmj.com/bmj/authors/checklists-forms/statisticians-checklist**).

A systematic review is a comprehensive high- level summary of primary research on a specific research question that attempts to identify, select , synthesise and appraise all (high quality) evidence relevant to that question. A meta-analysis uses statistical methods to quantitatively evaluate pooled data from single studies. Many pathological reviews are likely not to have sufficient data on clinical outcomes to warrant a meta-analysis.

While the content of a systematic review will be partly determined by the topic and evidence, as a minimum the review should:
• Clearly state the purpose of the review
• Determine inclusion and exclusion criteria to generate a PRISMA flowchart that includes identification of studies, screening, eligibility and inclusion data (See Liberati A, Altman DG, Tetzlaff J et al, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009: 339: b2700)
• Determine the primary end point of the review ie. acceptance or rejection of the null hypothesis
• Clearly describe the search methodology (databases, search terms)
• Describe the process of data extraction
• Undertake statistical assimilation if appropriate
• Evaluate the quality and/or risk of bias of the studies included preferably using a standard assessment tool (See Guyatt, GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924-926

Results
Present your results in logical sequence in the text, tables and illustrations. Do not repeat in the text all the data in the tables or illustrations; emphasise or summarise only important observations. Figures and tables should be clearly referred to in the manuscript. It is generally the case that interpretation should be reserved for the discussion.

Discussion

Emphasise the novel and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies including those that may conflict with the data you present. Highlight the clinical importance of your findings.
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Acknowledgements
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Chapter in an edited book

Dardick I. Histogenesis and morphogenesis of salivary gland neoplasms. In Ellis GL, Auclair PL, Gnepp DR eds. Surgical pathology of the salivary glands. Philadelphia, PA: WB Saunders, 1991; 108-128.

Chapter in a book

Ellis GL, Auclair PL. Tumours of the salivary glands. In Atlas of tumour pathology, 3rd edn. Washington DC: Armed Forces Institute of Pathology, 1996; 39-143.

Entry in a database

Online Mendelian Inheritance in Man [Internet]. Johns Hopkins University. Record No. 191170. Tumour Protein p53; TP53; [Accessed February 14, 2010]: Available from: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=191170

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