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Risk Factors for Oral Leukoplakia: A Meta-Analysis

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Abstract

Background: Oral leukoplakia is a frequent potentially malignant disorder of the oral mucosa. Its main etiological factors are tobacco and/or alcohol consumption and it is a lesion that may suffer malignant transformation.

Objective: To assess the possible risk factors related to oral leukoplakia.

Search Methods: A PubMed search through February 2018, using the following keywords was performed: "leukoplakia, oral" and "risk factors".

Selection Criteria: Studies with findings on risk factors for oral leukoplakia.

Data Analysis: The data were analyzed using statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For continuous outcomes, the estimates of effects of an intervention were expressed as Mean Difference (MD) using the Inverse Variance (IV) method and, for dichotomous outcomes; the estimates of effects of an intervention were expressed as Odds Ratios (OR) using Haenszel Mantel (HM) method, both with 95% confidence intervals.

Results: 14 studies on risk factors of OL were included in this meta-analysis. Main risk factors for OL were: high-risk HPV infection (OR: 6.03), any HPV infection (OR: 5.41), tobacco consumption (OR: 3.84), male gender (OR: 1.84) and age over 55 years-old (OR: 1.73).

Conclusions: HPV infection and tobacco consumption were the most important risk factors for oral leukoplakia.

Keywords: Oral leukoplakia; Precancerous conditions; Risk factors

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Introduction

Oral Leukoplakia (OL) is a potentially malignant disorder of the oral mucosa defined as "white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" [1]. OL is the most common potentially malignant disorder of the oral mucosa with a global prevalence estimated at around 2.60% [2].

Clinically it presents as a persistent white lesion with no pathognomonic histopathological features. The real potential for malignant transformation of OL is not yet well established [3]. According to different studies, the malignant transformation rate of OLs ranges from 0.13% to 34% [4]. Most of OLs are related to mainly tobacco and/or alcohol consumption. However, there are some OLs not associated with these harmful habits that are classified as idiopathic oral leukoplakias that have an even higher rate of malignant transformation [5]. The main risk factors related to OL are age, sex and, in the case of malignant transformation, the oral leukoplakias clinical type (homogeneous/non-homogeneous) and the degree of epithelial dysplasia of the lesion [2]. The aim of this study was to assess the possible risk factors related to oral leukoplakia.

Materials and Methods

A PubMed search of studies on risk factors related to oral leukoplakia to February 2018 was conducted. Search strategies included the combination of the following terms from the Medical Subjects Headings (MeSH): "leukoplakia, oral" [MeSH Terms] and "risk factors" [MeSH Terms]. The inclusion criteria were: a) type of studies (clinical trials, clinical studies, comparative studies and multicenter studies). All the studies had to have a patient group and a control group; b) studies with full-text availability.

After applying the inclusion criteria (type of studies, full-text availability) remained 43 studies. Twenty-nine studies were excluded for various causes (non-relevant data, inadequate allocation, problems in selection of participants, lack of an adequate control group). Finally, 14 studies were

Table 1: Descriptive characteristics of included studies of Oral Leukoplakia (OL).

Author	Year	Country	Study design	Type of population	OL cases	Controls	OL diagnosis	OL risk factors assessed
Hashibe [13]	2000	India	Case-control study	Rural population	927	47,773	Not specified	Age, Gender, Tobacco consumption, Alcohol consumption.
Macigo [18]	2001	Kenya	Case-control study	Rural population	85	141	WHO criteria	Tobacco consumption,
Dietrich [7]	2004	Germany	Cross-sectional survey	US general population	65	15,746	WHO criteria	Age, Gender, Tobacco consumption, Alcohol consumption, Diabetes.
Fisher [11]	2005	USA	Case-control study	Hospital population	90	78	Histopathologic examination	Age, Gender, Tobacco consumption, Alcohol consumption.
Dikshit [15]	2006	India	Case-control study	Rural population	927	47,773	WHO criteria	Gender, Diabetes, Hypertension.
Chen [17]	2006	Taiwan	Retrospective case-controlled study	Veterans General Hospital	36	22	Histopathologic examination	Tobacco consumption, HPV detection.
Szarka [19]	2009	Hungary	Retrospective case-controlled study	University Hospital population	44	72	Not specified	HPV detection.
Amarasinghe [14]	2010	Sri Lanka	Case-control study	Rural population	102	728	WHO criteria	Gender, Tobacco consumption, Alcohol consumption.
Meisel [9]	2010	Germany	Cross-sectional survey	General population	123	246	WHO criteria	Hypertension.
Meisel [16]	2012	Germany	Cross-sectional survey	General population	123	246	WHO criteria	Age, Gender, Tobacco consumption, Diabetes.
Chandroth [10]	2014	India	Cross-sectional survey	Fishermen	135	685	Not specified	Age, Gender, Tobacco consumption, Alcohol consumption.
Dalla-Torre [6]	2015	Austria	Case-control study	Hospital population	118	100	Histopathologic examination	Age, Gender, Tobacco consumption, Alcohol consumption, HPV detection.
Kaur [8]	2016	India	Case-control study	Hospital population	40	40	WHO criteria	Age.
Granero [12]	2017	Spain	Retrospective case-controlled study	University Hospital population	142	68	WHO criteria	Age, Gender, Tobacco consumption, Alcohol consumption.

WHO:World Health Organization; HPV: Human papillomavirus

Table 2: Risk factors studied for Oral Leukoplakia (OL).

Risk factor	n	Reference value	MD[a] / OR	95% CI	I^2	p value
Age						
Mean age	4	Higher in OL patients	1.16[a]	-0.11 , 2.43	33%	0.07
> 55 years-old	4	OL patients	1.73	1.36 , 2.20	39%	<0.001*
Gender	9	Males	1.84	1.49 , 2.28	75%	<0.001*
Tobacco consumption	10	Yes	3.49	1.99 , 6.10	94%	<0.001*
Alcohol consumption	7	Yes	1.54	0.81 , 2.91	92%	0.19
Human papillomavirus (HPV)						
HPV detection	3	Yes	5.41	1.46 , 19.97	80%	0.01*
Low-risk HPV types	3	Yes	1.47	0.27 , 8.00	57%	0.65
High-risk HPV types	3	Yes	6.03	2.27 , 15.99	57%	<0.001*
Diabetic patients	3	Yes	1.66	0.96 , 2.88	75%	0.07
Hypertensive patients	2	Yes	1.04	0.88 , 1.22	0%	0.66

n: Number of studies; MD: Mean difference; OR: Odds Ratio; 95% CI: 95% confidence interval; I^2: Higgins statistic for heterogeneity; *Statistically significant.

included in this meta-analysis (Figure 1).

Statistical analysis

For the meta-analysis, the data were processed with the statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For the continuous variables, the Inverse Variance (IV) was used for the Mean Difference (MD) with 95% Confidence Intervals (95% CI). For the dichotomous variables, the Odds Ratio (OR) was used with the Haenszel-Mantel Chi-square formula (HM) with 95% Confidence Intervals (95% CI). Heterogeneity was determined according to the p-values and the Higgins statistic (I^2). In cases of high heterogeneity, the random effects model was applied. The significance level was set at $p<0.05$.

Results

Table 1 presents the descriptive characteristics of the 14 included studies in the meta-analysis. The main risk factors analyzed for Oral Leukoplakia (OL) are shown in Table 2.

Four studies considered age as a possible risk factor for oral leukoplakia [6-9], found a higher mean age in patients with OL than in controls, although without statistically significant association (MD=1.16, 95% CI: -0.11, 2.43, p=0.07).

Another 4 studies analyzed whether an age above or below 55 years could influence the risk of developing OL [10-13]. An age over 55 years increased 1.73 times the risk for developing oral leukoplakia with highly significant differences (OR=1.73, 95% CI: 1.36, 2.20, p<0.001).

Nine studies examined the possible influence of the male gender on the risk of oral leukoplakia [6,7,10-16]. A 1.84-fold higher risk was found in males with OL with highly significant statistical differences (OR=1.84, 95% CI: 1.49, 2.28, p<0.001).

Harmful habits (tobacco and alcohol consumption) in patients with oral leukoplakia compared to controls without the lesion were also studied. Ten studies considered tobacco consumption in both patients with OL and controls [6,7,10-14,16-18]. Tobacco

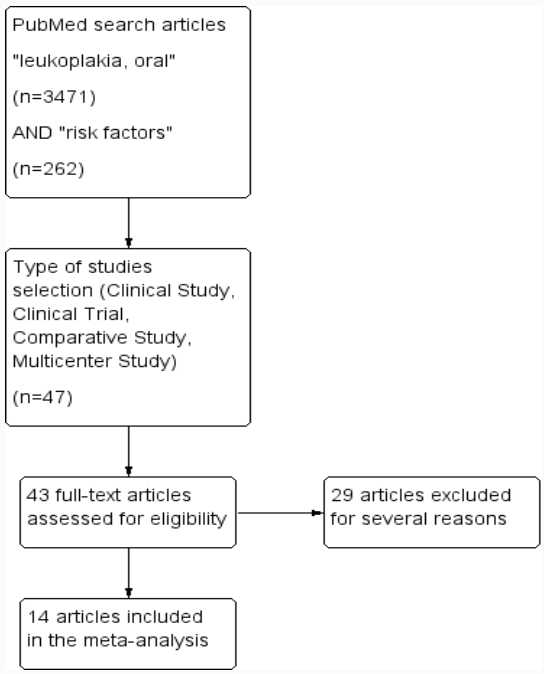

Figure 1: Study flow diagram.

consumption raised 3.49-fold the risk of OL with a highly significant association (OR=3.49, 95% CI: 1.99, 6.19, p<0.001). In other seven studies alcohol intake was assessed in both patients with OL and controls [6,7,10-14]. In this case, alcohol had no influence and the results found were not statistically significant (OR=1.54, 95% CI: 0.81, 2.91, p=0.19).

The possible involvement of Human Papillomavirus (HPV) in Oral Leukoplakias (OLs) was also assessed. Three studies assessed HPV detection in both patients and controls [6,17,19]. HPV-infected individuals had 5.41 times higher the risk for developing oral leukoplakia with statistically significant differences (OR=5.41, 95% CI: 1.46, 19.97, p=0.01). Differentiating between low-risk (types 6 and 11) and high-risk (types 16 and 18) HPV types in patients with OL and controls, low-risk HPV types had no relevant influence without statistically significant association (OR=1.47, 95% CI: 0.27, 8.00 p=0.65). In contrast, the high-risk HPV types infection raised 6.03-fold higher the risk of OL with a highly statistically significant association (OR=6.03, 95% CI: 2.27, 15.99, p<0.001).

The possible relationship between systemic diseases and oral leukoplakia was investigated too. Three studies considered diabetes in both patients with OL and subjects without OL [7,15,16]. A certain association was observed although no statistically significant differences were found (OR=1.66, 95% CI: 0.96, 2.88, p=0.07). Other two studies scrutinized the role of hypertension in both patients with OL and controls but with no statistically significant results (OR=1.04, 95% CI: 0.88, 1.22, p=0.66) [9,15].

Discussion

In the present meta-analysis on the possible risk factors related to Oral Leukoplakia (OL), data from 14 studies have been included.

Patients with OL had a mean age higher than controls evidencing a possible direct relationship between an older age and the risk for developing OL [6-9]. According to our study, subjects older than 55 years were 1.73 times more likely to developing OL (p<0.001). Four studies agreed with our results [10-13], finding a higher prevalence of OL in patients older than 55 years. In general, there was a higher prevalence of oral lesions including OL in the older population groups compared to younger groups. Probably the early-age of initiation of harmful habits (consumption of tobacco and/or alcohol) is one of the principal factors that justify the appearance of these lesions in older people [10].

In this study, the possible influence of sex with respect to oral leukoplakia was also analyzed with a higher prevalence in males. In fact, men were 1.84 times more likely to developing OL. Eight studies [6,7,10-15], four of them with statistically significant differences [6,7,13,14], coincided with our results. This predilection for OL by males could be explained by tobacco consumption, the main etiological factor related to OL [15]. Both oral leukoplakia and the rest of potentially malignant disorders of the oral mucosa are much more common in males, especially in large smokers [12]. However, most of the studies performed in patients with OL had higher proportions of male population than female and, in some of them; there is no histological confirmation of OL [16].

Tobacco consumption is considered as the most important etiological agent in oral leukoplakia. In the present meta-analysis, smoking patients were 3.49 times more likely to developing OL, with a highly statistically significant association (p<0.001). According to our results, eight studies confirmed the relevance of tobacco consumption as an etiological agent of OL [6,7,12-14,16-18]. Furthermore, the risk of developing OL is clearly associated with the type of consumption, the amount consumed and the age of onset of the habit. In Western countries, OL is associated with cigarette smoking, non-smoked tobacco (snuff) and alcohol drinking [14], while in Southeast Asia it is related to betel quid consumption [17]. The action of both tobacco and many other carcinogens is very influenced by time of exposition. This is the reason that justifies the higher prevalence of this lesion in older populations and is a wake-up call when it appears in younger populations with a shorter time of exposure to these agents [6,7]. India is the country with the highest prevalence of OL, a fact that is probably due to the consumption of betel quid and the dangerous habit of keeping this betel quid inside the oral cavity over the night [13].

Regarding alcohol consumption, in the present study, no statistically significant influence of this harmful habit was found in the risk for developing OL (p=0.19). Other studies that considered this factor found apparently conflicting results. In five studies a greater number of drinkers were observed among patients with OL [7,14,11-13], meanwhile, in other two studies there was a greater number of drinkers among the subjects without OL [6,10]. Nevertheless, in these studies, the amount of alcohol consumed was not determined, only the presence or not of the alcohol consumption. Alcohol by itself, independently of tobacco consumption, is an etiological factor related to OL. Amarasinghe et al. [14] pointed out that the weekly intake of alcohol was a factor that increased the risk of OL up to 3.5 times. Moreover, a combined consumption of tobacco and alcohol raised this risk to 14.3 times. Alcohol is a solvent that can damage cells and promote the tissue penetration by other carcinogens. Prolonged alcohol consumption increases the levels of cytochrome P-450 that contribute to the activation of the tobacco carcinogens enhancing the cumulative action of these harmful substances. In addition, alcohol can interact with several microorganisms related to OL, such as HPV or Candida albicans, inducing dysplastic changes in these lesions and worsening their biological behavior [13].

In this meta-analysis, HPV-infection increased 5.41 times the probability of developing OL (p=0.01). According to our result, three studies that examined the role of HPV infection in OL found statistically significant differences too [6,17,19]. In low-risk HPV types infection, in our study, there was no statistically significant influence (p=0.65) of HPV types 6, 11 in OL. The other studies that evaluated this parameter found opposite results, one found higher prevalence in patients with OL and other [6,19], higher prevalence in controls. In contrast, in the case of high-risk HPV (types 16 and 18), HPV infection increased 6.03 times the risk of OL (p<0.001). All the studies supported our results [6,17,19], confirming a significantly higher prevalence of high-risk HPV types in patients with OL. However, should be considered that the HPV detection in oral tissues is very conditioned by the detection technique used. More sensitive tests such as PCR increase the percentages of HPV detection. This could lead to an overestimation of the importance of HPV infection on oral lesions since the detection of a very small number of DNA copies would give a positive result [17]. High-risk HPV infections may promote several tissue changes that increase the risk of malignant transformation of OL [6]. Perhaps, HPV infection by itself does not induce dysplastic changes on the oral mucosa, but in conjunction with other factors may lead to them [19].

The possible relationship between some systemic diseases and Oral Leukoplakia (OL) was also analyzed. In this meta-analysis, neither diabetes (p=0.07) nor hypertension (p=0.66) had a significant influence on the risk of OL. Two studies found significant results with a higher number of diabetic patients with OL [7,16]. Diabetes increased almost 3 times the risk of OL [7], although currently, the true influence of this disease on OL is not yet clear.

All findings of this meta-analysis must be interpreted with caution due to the high heterogeneity of the studies included and the presence of different bias. The differences among studies could be conditioned by the study design, the methods used to collect data, the type of analysis used, the characteristics of the study populations and samples or the duration of the studies.

Conclusions

In this meta-analysis, the factors of greatest risk of oral leukoplakia were: high-risk HPV infection (OR: 6.03), any HPV infection (OR: 5.41), tobacco consumption (OR: 3.84), male gender (OR: 1.84) and age over 55 years old (OR: 1.73). Alcohol intake, low-risk HPV infection; the presence of diabetes and/or hypertension were factors without significant influence on the risk of oral leukoplakia.

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