Reviews

CLINICOPATHOLOGICAL PARAMETERS RELATED TO MALIGNANT TRANSFORMATION OF ORAL LEUKOPLAKIA: A META-ANALYSIS

ABSTRACT

Objective: To assess the clinical-pathological factors related to the malignant transformation of oral leukoplakia.

Materials and Methods: A search for articles on malignant transformation factors related to oral leukoplakia was conducted in the following electronic databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS) and Google Scholar. Thirty-seven articles with a low-moderate risk of bias according to the Newcastle-Ottawa methodological quality scale were included in this meta-analysis. The data were analyzed using the statistical programs RevMan 5.4 (The Cochrane Collaboration, Oxford, UK) and MedCalc Statistical Software version 16.4.3 (MedCalc Software Ltd. Ostend, Belgium) programs. The estimated prevalence was calculated according to DerSimonian and Laird random method. For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratios (OR) using the Mantel-Haenszel (M-H) method with 95% confidence intervals.

Results: The estimated global prevalence of malignant transformation of oral leukoplakia was 9.15%. The factors with the highest malignant transformation risk of oral leukoplakia were: non-homogeneous clinical types (OR: 5.41; p<0.001); leukoplakias with moderate-severe dysplasia (OR: 3.43; p<0.001); lesions located on the tongue and/or the floor of the mouth (OR: 3.19; p<0.001); leukoplakias in non-smokers (OR: 2.08; p<0.001) and lesions in women (OR: 1.73; p<0.001). In contrast, older age or regular alcohol intake were factors without significant influence (p>0.05).

Conclusions: Non-homogenous oral leukoplakias and with moderate-severe dysplasia are those with the highest probability of malignant transformation.

Keywords: Cell transformation, neoplastic, epidemiology, leukoplakia oral, risk factors.

*Alberto Rodriguez-Archilla[1]
Cristina Fuentes-Perez[2]

ORCID IDs of the authors:
A.R.A.   0000-0003-1023-943X
C.F.P.   0000-0002-5764-1525

[1] Department of Stomatology, Oral Medicine Unit. Faculty of Dentistry. University of Granada, Granada (Spain).

INTRODUCTION

In 2005, the World Health Organization (WHO) in collaboration with the UK Center for Oral Cancer and Precancer carried out a redefinition of oral leukoplakia (OL) as a "white plaque of questionable risk whose diagnosis is reached having excluded other known diseases or disorders that do not involve an increased cancer risk".[1]

OL is the most common potentially malignant disorder of the oral mucosa with an overall prevalence of around 2.6%.[2] Clinically, two main clinical forms are differentiated: a) homogeneous, with uniform white lesions and b) non-homogeneous, within which three types are distinguished: speckled, nodular and verrucous.[3] Its true potential for malignancy is not yet well established and is under constant analysis. Most oral leukoplakias are related to tobacco and/or alcohol consumption. However, idiopathic leukoplakias not associated with these factors have a higher rate of malignant transformation. According to different studies, the OL malignant transformation rate ranges between 0.13% and 34%.[4] The purpose of this study was to assess the clinicopathological factors related to the malignant transformation of oral leukoplakia.

MATERIALS Y METHODS

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a search for studies on risk factors for malignant transformation of oral leukoplakia was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS) and Google Scholar. Search strategies included a combination of Medical Subjects Headings (MeSH) and free-text terms. The search terms were as follows: "leukoplakia, oral" [MeSH Terms] AND ("cell transformation, neoplastic" [MeSH Terms] OR "malignant" [All Fields] OR "transformation" [All Fields] OR "degeneration" [All Fields] OR "progression" [All Fields]); "Oral", "leukoplakia" AND "malignant"; allintitle: "malignant", "oral leukoplakia". After this initial search, 2994 articles were found (1029 in PubMed, 1867 in WoS and 98 in Google Scholar), 1792 of them duplicates, leaving 1202 articles for review. Article titles and abstracts were examined independently by two authors (ARA and CFP) that selected jointly the articles to include in the present study. The exclusion criteria were: a) articles without full-text availability (n=563); b) articles with a score of fewer than 6 stars out of a maximum of 9 on the Newcastle-Ottawa methodological quality assessment scale[5] (n=134), and c) studies with non clinical or non-usable data (n=468). Finally, 37 studies were included in the meta-analysis (Figure 1).
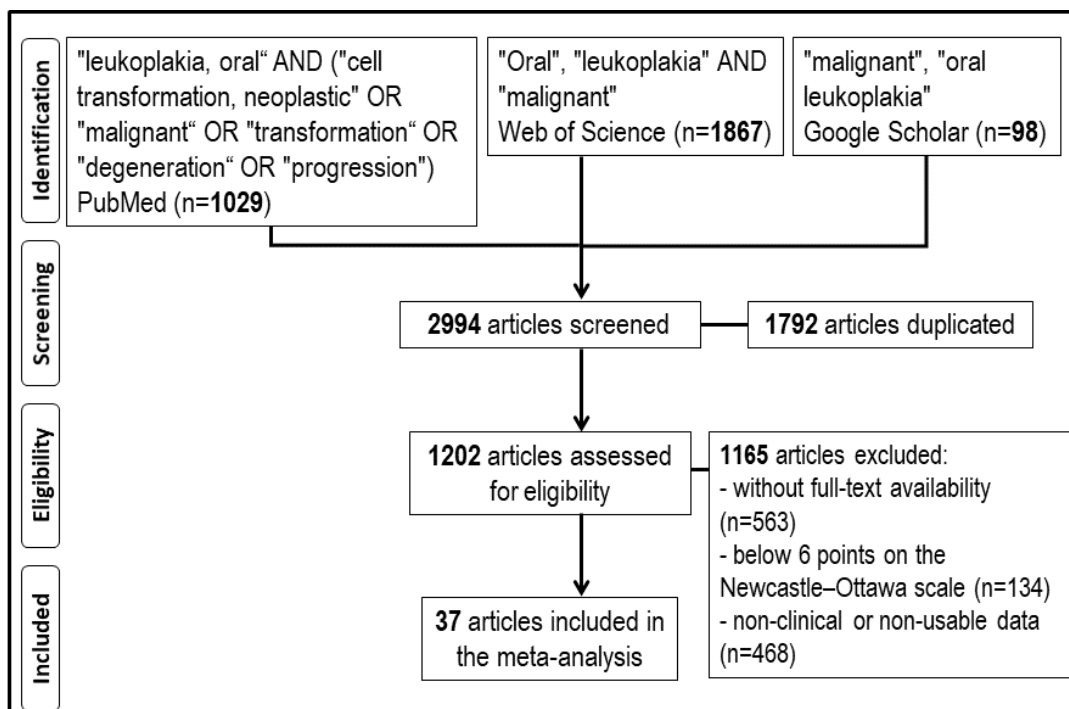

Figure 1. Study flow diagram.

Statistical Analysis

Data were statistically analyzed with the RevMan 5.4 (The Cochrane Collaboration, Oxford, UK) and MedCalc Statistical Software version 16.4.3 (MedCalc Software Ltd. Ostend, Belgium) programs. The estimated prevalence was calculated according to DerSimonian and Laird random method. For dichotomous outcomes, the odds ratio (OR) with the Mantel-Haenszel Chi-square formula (M-H) and 95% confidence intervals (95% CI) was used. Heterogeneity was determined according to the P values, Cochran's Q, and Higgins statistic (I^2). A random-effects model was applied if the heterogeneity was high ($I^2 > 50\%$). The minimum level of significance was set at $p < 0.05$.

RESULTS

Table 1 presents the thirty-seven studies[6-42] that analyzed the prevalence of malignant transformation of oral leukoplakia in populations from 15 different countries. The estimated global prevalence of malignant oral leukoplakia was 9.15% (95% CI: 6.71 to 11.93%) with a range from the maximum prevalence of 34.00% (95% CI: 21.20 to 48.76%)[24] to the minimum of 0.12% (95% CI: 0.04 to 0.27%).[10]

Table 1. Studies on the prevalence (and 95% CI) of malignant transformation of oral leukoplakia

Study	Year	Country	Sample size	Prevalence	(95% CI)
Einhorn[6]	1967	Sweden	782	1.53%	(0.79 to 2.66%)
Pindborg[7]	1968	Denmark	214	5.14%	(2.59 to 9.01%)
Gangadharan[8]	1971	India	1411	4.46%	(3.44 to 5.67%)
Roed-Petersen[9]	1971	Denmark	331	2.71%	(1.25 to 5.09%)
Silverman[10]	1976	India	4762	0.12%	(0.04 to 0.27%)
Banoczy[11]	1977	Hungary	670	5.97%	(4.29 to 8.04%)
Kramer[12]	1978	UK	29	24.13%	(10.29 to 43.54%)
Pogrel[13]	1979	UK	19	15.78%	(3.38 to 39.57%)
Gupta[14]	1980	India	735	1.63%	(0.84 to 2.83%)
Roch-Berry[15]	1981	UK	117	17.09%	(10.76 to 25.15%)
Silverman[16]	1984	USA	257	17.51%	(13.06 to 22.71%)
Lind[17]	1987	Norway	157	8.91%	(4.96 to 14.50%)
Hogewind[18]	1989	Netherlands	46	6.52%	(1.36 to 17.89%)
Shi[19]	1992	China	235	13.61%	(9.50 to 18.67%)
Schepman[20]	1998	Netherlands	166	12.04%	(7.51 to 17.99%)
Ge[21]	1999	China	211	6.63%	(3.67 to 10.88%)
Saito[22]	1999	Japan	111	7.20%	(3.16 to 13.70%)
Guan[23]	2001	China	110	11.81%	(6.44 to 19.36%)
Napier[24]	2003	UK	50	34.00%	(21.20 to 48.76%)
Mishra[25]	2005	India	2920	0.68%	(0.41 to 1.05%)
Lee[26]	2006	Taiwan	1046	12.90%	(10.93 to 15.09%)
Hsue[27]	2007	Taiwan	913	3.61%	(2.50 to 5.03%)
Arduino[28]	2009	Italy	207	7.24%	(4.11 to 11.67%)
Lan[29]	2009	China	409	12.71%	(9.64 to 16.33%)
Zhu[30]	2009	China	150	9.33%	(5.19 to 15.16%)
Liu[31]	2010	China	218	17.89%	(13.04 to 23.63%)
Wang[32]	2011	China	576	11.45%	(8.97 to 14.34%)
Warnakulasuriya[33]	2011	UK	335	6.86%	(4.40 to 10.12%)
Brzak[34]	2012	Croatia	54	1.85%	(0.04 to 9.89%)
Gao[35]	2012	China	1832	4.64%	(3.72 to 5.70%)
Ho[36]	2012	UK	91	25.27%	(16.74 to 35.47%)
Liu[37]	2012	China	320	17.81%	(13.77 to 22.45%)
Lian[38]	2013	Taiwan	1238	7.10%	(5.74 to 8.68%)

Brouns[39]	2014	Netherlands	144	11.11%	(6.48 to 17.41%)
Kil[40]	2016	South Korea	27	25.92%	(11.11 to 46.28%)
Wang[41]	2018	Taiwan	1046	12.90%	(10.93 to 15.09%)
Gandara-Vila[42]	2018	Spain	85	8.23%	(3.37 to 16.23%)
Total (*random effects*)			**22024**	**9.15%**	**(6.71 to 11.93%)**

Test for heterogeneity
Q=1480.19; df: 36 (P<0.0001); I²=97.57%; 95% CI: (97.15 to 97.92)

UK: United Kingdom; **USA:** United States of America; **%:** percentage; **(95% CI):** 95% confidence interval.

The main risk factors related to the malignant transformation of oral leukoplakia are shown in Table 2.

Table 2. Main risk factors related to malignant transformation of oral leukoplakia (OL)

Risk factor	n	Outcome	OR	(95% CI)	I²	p-value
Age	6	>60 years-old	1.56	(0.95 to 2.57)	46%	0.08
Gender	22	Female	1.73	(1.47 to 2.05)	21%	<0.001*
OL clinical type	13	Non-homogeneous	5.41	(3.24 to 9.02)	61%	<0.001*
Degree of dysplasia	6	Moderate-Severe	3.43	(2.30 to 5.11)	0%	<0.001*
OL Location	9	Tongue- FM	3.19	(2.26 to 4.50)	41%	<0.001*
Smoking	6	Non-smoker	2.08	(1.51 to 2.80)	0%	<0.001*
Drinking	6	Non-drinker	1.02	(0.76 to 1.38)	0%	0.87

n: number of studies; **OR:** Odds Ratio; **(95% CI):** 95% confidence interval; **I²:** Higgins statistic for heterogeneity (percentage); **FM:** floor of the mouth; *statistically significant.

Six studies[11,28,31,33,37,42] examined the possible influence of age on the oral leukoplakia (OL) malignant transformation risk. Although the malignant transformation of the oral leukoplakia was more frequent in those older than 60 years, age was a factor without influence on the OL malignancy. After statistical analysis, no significant relationship was observed (OR=1.56; 95% CI: 0.95 to 2.57; p=0.08).

Twenty-two studies[7,9-11,13,15-20,24,26,28-33,35,37,40] considered gender as a possible OL malignant transformation risk factor. Women were 1.73 times more likely to present malignant leukoplakias compared to men, finding a highly significant statistical association (OR=1.73; 95% CI: 1.47 to 2.05; p<0.001).

Thirteen studies[11,14,17-19,24-26,28-30,36,37] assessed the clinical type of oral leukoplakia (OL). Non-homogeneous OL had a 5.41-fold increase in the risk of malignant transformation compared to homogeneous ones, with highly significant statistical differences (OR=5.41; 98% CI: 3.24 to 9.02; p <0.001).

Six studies[20,28,33,36,37,43] analyzed the degree of epithelial dysplasia of oral leukoplakias (OLs). Moderate-severe dysplasia OLs were 3.43 times more likely to malignant transformation than mild dysplasia OLs. After statistical analysis, a highly significant relationship was found (OR=3.43; 95% CI: 2.30 to 5.11; p<0.001).

Nine studies[11,20,25,26,28,31,37,39,42] determined the oral leukoplakias malignant transformation risk based on the location of the lesions. Oral leukoplakias located on the tongue and/or floor of the mouth increased 3.19 times the risk of malignant transformation with a highly significant statistical association (OR=3.19; 95% CI: 2.26 to 4.50; p<0.001).

Six studies[26,28,31,37,39,42] evaluated the role of harmful habits, both tobacco consumption and alcohol intake, on the malignant transformation risk of oral leukoplakia (OL). Non-smoking patients with oral leukoplakias had 2.08 times more risk, observing highly significant statistical differences (OR=2.08; 95% CI: 1.54 to 2.80; p<0.001). The alcohol intake had no significant effect on the OL malignant transformation probability (OR=1.02; 95% CI: 0.76 to 1.38; p=0.87).

DISCUSSION

Data from thirty-seven studies on the clinicopathological factors related to malignant

transformation of oral leukoplakia have been considered in the present meta-analysis.

In this paper, the estimated global prevalence of malignant transformation of oral leukoplakia was 9.15% (95% CI: 6.71 to 11.93%). Warnakulasuriya *et al.*[4] conducted a systematic review of 24 studies in which they analyzed the rate of malignant transformation of oral leukoplakias, finding 405 malignant cases (3.5%) out of a total of 11423 leukoplakias, a prevalence rate lower than that observed in our study.

In the present study, an older age did not imply a greater risk of malignant transformation of oral leukoplakias, without a statistically significant relationship (p=0.08). Of the six studies that examined age, five of them[11,28,31,33,37] observed more malignant lesions in patients older than 60 years and only one,[42] in those younger than this age. The findings of the different studies on the role of age were highly variable. Some researchers argue that age is not a risk factor,[31] while others state that the patient's age is an important risk factor that affects malignant transformation and that it may be correlated with individual genetic susceptibility.[37] There is no clear evidence that older age increases the probability of malignant progression in oral leukoplakia. Older people, probably due to immune dysfunction and long-term exposure to other associated risk factors, may be more susceptible to malignancy.[4]

In the present study, women were 1.73 times more likely to present malignant oral leukoplakias with a highly significant statistical association (p<0.001). Of the 22 studies that considered gender, nineteen[7,9-11,16-20,24,26,29-33,35,37,40] agreed to observe more malignant lesions in women; meanwhile, three of them[13,15,28] observed it more in men. Most of these studies indicate that females' oral leukoplakias have a higher risk of malignant transformation. Although oral leukoplakia is relatively uncommon in women compared to men, the malignant transformation of leukoplakia is significantly higher in women. The reason why females are more predisposed to the malignant transformation of its lesions remains a paradox.[4] Moreover, an increased risk of malignant transformation of oral leukoplakia has been observed in non-smoking women. It is not clear either why the absence of smoking habit is associated with an increased risk of malignant transformation only in women.[20]

In this study, non-homogeneous oral leukoplakias increased 5.41-fold their risk of malignancy, observing highly significant statistical differences (p<0.001). Twelve studies[11,14,17,19,24-26,28-30,36,37] pointed out a higher probability of malignancy in non-homogeneous oral leukoplakias. Similarly, a higher degree of dysplasia (moderate-severe) raised 3.43-fold the probability of malignancy, with a highly significant relationship (p<0.001). Of the 6 studies that examined the degree of dysplasia, five of them[20,28,33,36,37] showed a higher risk of malignancy in the most dysplastic leukoplakias and only one[43] did not observe this fact, without statistically significant results. Almost all studies claim that non-homogeneous oral leukoplakias show a higher malignant transformation risk compared to homogeneous leukoplakias that appear to follow a more benign course. In non-homogeneous lesions, it is important an adequate choice of the biopsy site since it will condition its correct diagnosis, as well as a more aggressive treatment for this type of leukoplakias. Lee *et al.*[26] in their study of 1046 oral leukoplakia found that non-homogeneous lesions were 5.69 times more likely to present epithelial dysplasia and 28.13 times more likely to malignant transformation. 72.6% of the non-homogeneous leukoplakias and 33.3% of the homogeneous ones were dysplastic lesions. Malignant transformation of non-homogeneous oral leukoplakias approached 20% in contrast to less than 1% in homogeneous leukoplakias. Classifying the grade of dysplasia as: no dysplasia, mild, moderate, and severe, lends itself to some subjectivity in interpretation by pathologists and could distort the results. Therefore, in an attempt to unify criteria, a classification into two categories has been proposed: a) no/questionable/mild - low-grade dysplasia and b) moderate/severe - high-grade dysplasia). High-grade dysplasias are closely associated with an increased malignant transformation risk and in shorter periods. This justifies periodic follow-up during the first 2-3

years for patients with high-grade dysplastic oral leukoplakias to be able to detect early events of malignant transformation.[37]

In this study, oral leukoplakias located on the tongue and/or floor of the mouth were 3.19 times more likely to suffer malignant transformation with a highly significant statistical association (p<0.001). The nine studies[11,20,25,26,28,31,37,39,42] that focused on the location of oral leukoplakia, showed that the lingual location and/or on the floor of the mouth were the ones with the highest risk of malignant transformation. In a systematic review, the most frequent locations of malignant oral leukoplakias were the tongue (24.22% of cases) and the floor of the mouth (14.85%).[4] Lee *et al.*[26] found that leukoplakias located on the tongue and/or the floor of the mouth increased 1.84 times the probability of epithelial dysplasia and 2.72 times the risk of malignancy compared to leukoplakias with other locations. Severe dysplastic lesions tended to be located on the ventrolateral lingual surface and the floor of the mouth, showing greater potential for malignant transformation and a greater frequency of loss of heterozygosity in chromosomes 3p, 9p and 17p. A possible explanation for this higher risk in these locations would be that these areas are substantially more exposed to local carcinogens due to the greater permeability of the oral mucosa.[42]

In the present investigation, surprisingly non-smokers had an increase of 2.08 times the malignant transformation risk of their leukoplakias with highly significant statistical differences (p<0.001). Regular alcohol consumption did not have a significant impact on the malignancy of oral leukoplakia, without reaching statistical significance (p=0.87). All studies[26,28,31,37,39,42] indicated an increased malignant risk in leukoplakias from non-smoking subjects. In the case of alcohol intake, three of them[26,37,42] found a higher malignant transformation risk in lesions from non-drinkers, compared to another three[28,31,39] who did show it in lesions from drinkers. However, none of the results of these studies was statistically significant. The tobacco and/or alcohol consumption play an important role in the development of oral leukoplakia, although their role in its malignant transformation remains controversial and it has not been clarified yet.[37] Smoking and drinking are well-established risk factors for dysplastic oral leukoplakia and oral cancer, but not for the malignant transformation risk from leukoplakia. Various studies show that smoking-related oral leukoplakias appear to have less malignant potential than those not associated with smoking. The reasons for these seemingly paradoxical findings remain unclear. Several possible explanations could be raised: 1) in the absence of tobacco and/or alcohol as stimulating agents, there are other more potent carcinogenic factors; 2) since carcinogenesis is a multistep process, the factors that condition the development of oral leukoplakias would be different from the factors responsible for the malignant transformation of these lesions; 3) the lower malignant transformation risk of leukoplakias among smokers/drinkers could be justified in that the oral carcinogenesis process is more prolonged in non-smokers/abstainers and, therefore, the evolution time of oral leukoplakias is longer predisposing them to malignancy.[26]

This study has some limitations. The periods of follow-up of the lesions are highly variable in the different studies. In some of them, they are too short and there is probably an underestimation of cases of malignancy. Considering the harmful habits, on some occasions, the quantity and age of the habit, as well as the alcohol content of the beverages, could not be adequately evaluated. The influence of superinfection of oral leukoplakias by human papillomavirus (HPV) and/or *Candida* species could not be analyzed either.

Finally, the high heterogeneity observed in some comparisons of this meta-analysis demands a cautious interpretation.

CONCLUSIONS

In this study, the estimated global prevalence of malignant transformation of oral leukoplakia was 9.15%. The factors with the highest malignant transformation risk of oral leukoplakia were: non-homogeneous clinical types (OR:5.41; p<0.001); leukoplakias with moderate-severe dysplasia (OR:3.43; p<0.001); lesions located on the tongue

and/or the floor of the mouth (OR:3.19; p<0.001); leukoplakias in non-smokers (OR:2.08; p<0.001) and lesions in women (OR:1.73; p<0.001). In contrast, older age or regular alcohol intake were factors without significant influence (p> 0.05).

CONFLICTS OF INTEREST STATEMENT

No conflicts of interest.

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