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Review

Malignant transformation risk of oral lichen planus: A systematic review and comprehensive meta-analysis

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ABSTRACT

Objectives: To evaluate current evidence on the malignant transformation of oral lichen planus (OLP), oral lichenoid lesions (OLLs), and oral lichenoid reactions (LRs) and to determine the variables with greatest influence on cancer development.

Material and methods: We searched PubMed, Embase, Web of Science, and Scopus for studies published before November 2018. We evaluated the quality of studies (QUIPS tool). We carried out meta-analyses to fulfill our objectives. We examined the between-study heterogeneity and small-study effects, and conducted sensitivity studies and subgroup analyses.

Results: Inclusion criteria were met by 82 studies (26,742 patients. The combined malignant transformation rate was 1.14% for OLP (95% CI = 0.84–1.49), 1.88% for OLLs (95% CI = 0.15–4.95) and 1.71% for LRs (95% CI = 0.00–5.46). Subgroup analysis revealed a higher malignant transformation rate in studies when the presence of epithelial dysplasia was not an exclusion criterion ($p = 0.001$), when both clinical and histopathological criteria were used for diagnosis ($p < 0.001$), when the follow-up was at least 12 months ($p = 0.048$), and when there was lower risk of potential bias ($p = 0.002$). Malignant transformation risk factors were: tongue localization (RR = 1.82, 95% CI = 1.21–2.74, $p = 0.004$), presence of atrophic-erosive lesions (RR = 4.09, 95% CI = 2.40–6.98, $p < 0.001$), tobacco use (RR = 1.98, 95% CI = 1.28–3.05, $p = 0.002$), alcohol consumption (RR = 2.28, 95% CI = 1.14–4.56, $p = 0.02$), and hepatitis C virus infection (RR = 4.46, 95% CI = 0.98–20.22, $p = 0.053$).

Conclusions: The malignant transformation rates of OLP, OLLs and LRs are underestimated due essentially to restrictive diagnostic criteria, inadequate follow-up periods, and/or low quality of studies.

Introduction

Oral lichen planus (OLP) is an autoimmune chronic inflammatory disease of unknown etiology, characterized by the presence of white reticular lesions sometimes accompanied by erosive and/or atrophic lesions [1]. Most authors consider it a highly prevalent disorder that may develop in up to 2% of the general population [2]. OLP is currently considered an oral potentially malignant disorder (OPMD), although its malignant transformation rate is controversial, largely attributable to the restrictive criteria for its diagnosis [3]. The modified WHO criteria for OLP diagnosis [4] proposed by Van der Meij and Van der Waal [5] are widely followed by clinicians and researchers. These criteria require the clinical appearance of relatively symmetrical bilateral white reticular lesions with histopathological signs of liquefaction degeneration of the basal epithelial cell layer, a well-defined band-like zone of lymphocytic infiltration confined to the superficial chorion, and the absence of epithelial dysplasia. Cases that fail to meet all of these criteria are designated as oral lichenoid lesions (OLLs) and in the view of the above authors [5], are attributed with a premalignant character, whereas OLPs are not [6]. Questions have been raised about epithelial dysplasia as OLP exclusion diagnostic criterion [3], given that the presence of dysplasia, especially severe dysplasia, is the gold standard

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for prediction of malignant transformation in OPMDs [7]. Therefore, the adoption of dysplasia as an exclusion criterion would likely select cases at lower risk of malignant transformation, with a consequent underestimation of the malignant potential of this prevalent disease [3,8–10]. In addition, most studies to date have not provided precise information on variables that might influence malignization, such as the type of lesion, its oral localization, or habits associated with oral cancer development, e.g., tobacco and alcohol consumption. Finally, there appears to be a marked lack of knowledge about the malignant transformation potential of oral lichenoid reactions (LRs), which are clinically related to OLP and have well-established etiologies, including drug consumption or contact of the oral mucosa with dental restorative materials, mainly silver amalgam, with some authors also reporting their potential association with oral cancer [11,12].

With this background, our objective was to qualitatively and quantitatively evaluate available scientific evidence on the malignant transformation of OLP, OLLs, and oral LRs in a systematic review and meta-analysis of 82 studies (26,742 patients) in order to precisely estimate their malignant transformation rates, explore influential variables, determine key predictive factors for progression to cancer, and identify clinical approaches to reduce the risk of malignization.

Material and methods

This systematic review and meta-analysis complies with PRISMA and MOOSE guidelines [13,14], and its preparation followed criteria of the *Cochrane Handbook for Systematic Reviews of Interventions* [15], *Centre for Reviews and Dissemination (CRD)'s guidance for undertaking reviews in health care* [16], and *Cochrane Prognosis Methods Group* [17].

Protocol

In order to minimize risk of bias and improve the transparency, precision, and integrity of our systematic review and meta-analysis, a protocol on its methodology was registered *a priori* in *PROSPERO international prospective register of systematic reviews* (www.crd.york.ac.uk/PROSPERO, registration number CRD42019128539) [18]. The protocol followed PRISMA-P reporting guidelines in order to ensure rigor [19].

Search strategy

We searched Pubmed, Embase, Web of Science, and Scopus databases for studies published before the search date (November 2018), with no lower date limit. Searches combined database thesaurus terms (e.g., MeSH and EMTREE) and free terms, constructed to maximize sensitivity (Table S1, Appendix p3). We also manually screened the reference lists of retrieved studies for further relevant studies. All references were managed using Mendeley v.1.17.10 (Elsevier. Amsterdam, The Netherlands); duplicate references were eliminated.

Eligibility criteria

Eligibility criteria were independently applied by two authors (MAGM and PRG). Any disagreement was resolved by consensus.

Inclusion criteria: (1) Original research studies published in English on the OLP malignant transformation rate. (2) Longitudinal study design. (3) In the case of results derived from the same study population, we included the most recently reported or those providing more data; the use of the same population in different studies was determined by verifying the name and affiliation of authors, treatment hospital, and recruitment period.

Exclusion criteria: (1) Reviews, retracted articles, meta-analyses, case reports, editorials, letters, abstracts of scientific meetings, personal opinions or comments, book chapters, and any study in a language other than English. (2) *In vitro* or animal experimental studies. (3) Studies that do not analyze the OLP malignant transformation rate or provide insufficient data for its calculation. (5) Studies with cross-sectional design and no patient follow-up data. (6) Studies that do not differentiate between oral and cutaneous lichen planus or lesions from other anatomical sites.

Articles were selected in two phases by the two authors (MAGM and PRG), first screening titles and abstracts for those apparently meeting inclusion criteria, and then reading the full text of selected articles for their final inclusion or exclusion.

Data extraction

Two authors (MAGM and PRG) independently extracted data from the selected articles for standardized full-text analysis, using Excel v.2015 spreadsheets (Microsoft. Redmond, WA, USA). These data were additionally reviewed by two different authors (IRA and LGR), resolving discrepancies by consensus. We recorded the first author, year of publication, country, study design, sample size, number of malignant transformation cases, recruitment and follow-up periods, diagnostic criteria, localization and clinical appearance of lesions, the sex, age, tobacco and alcohol consumption and diet of patients and the presence of any systemic disease, as well as treatment received for OLP and LRs.

Evaluation of quality and risk of bias

Quality was assessed by two authors (MAGM and PRG) using the *Quality in Prognosis Studies* (QUIPS) tool (*Cochrane Prognosis Methods Group)* [20], which considers the following domains: [1] Study participation, [2] Study attrition, [3] Prognostic Factor Measurement, [4] Outcome Measurement, [5] Study confounding, and [6] Statistical Analysis and Reporting) [21]. The risk of bias was qualified as low, moderate, or high for each domain. Discrepancies were resolved by consensus.

Statistical analysis

OLP and LR malignant transformation rates were estimated in the meta-analysis by combining proportions and their corresponding 95% confidence intervals (CIs). Proportions in individual studies were calculated by extracting crude numerators (malignant transformation cases) and denominators (total number of OLP cases). The 95% CI was calculated for each study and for combined estimations, based on the score-test statistic [22]. The influence of studies with extremely small values (0 or close to 0) was minimized by using Freeman-Tukey double-arcsine transformation to stabilize the variance of proportions [23]. Combined proportions were estimated with a random effect model (Der Simonian and Laird method). Further meta-analyses were performed to establish the capacity of patient variables (sex, age, localization and clinical appearance of lesions, habits, and systemic disease) to predict the risk of progression to cancer. These meta-analyses were performed by combining relative risks (RR) and corresponding 95% CIs using both fixed-effect (Mantel-Haenszel method) and random-effect (DerSimonian and Laird method) models. Forest plots were constructed for the graphic representation of combined estimations and their subsequent analysis.

Cochran's Q test (based on the chi-square test) was used to assess the between-study heterogeneity [24]; given its low statistical power, $p < 0.1$ was considered significant, assuming apparent heterogeneity. The Higgins I^2 statistic was also used to quantify the percentage heterogeneity, with results of 25, 50, and 75% indicating low, moderate, and high heterogeneity, respectively [24,25].

Subgroup analyses were performed, stratifying by diagnostic criteria, follow-up period, geographical region and risk of potential bias, in order to identify possible sources of heterogeneity and determine the malignant transformation rate in these subgroups.

Sensitivity analyses were conducted to test the reliability of combined results, evaluating the influence of each individual study on the

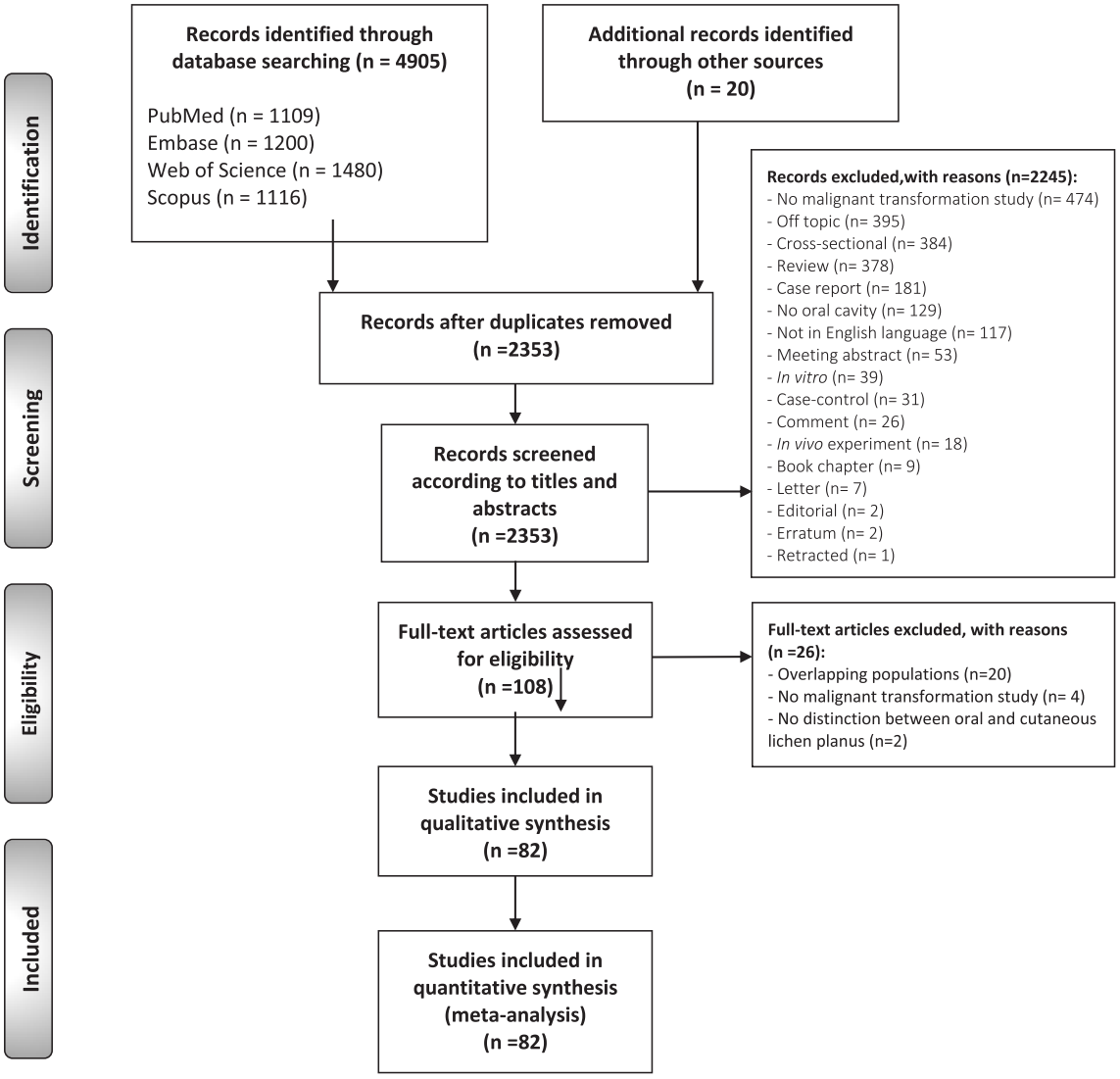

Fig. 1. Flow diagram of the identification and selection of studies that address the malignant transformation rate of OLP, OLLs and LRs.

general estimation of the malignant transformation rate [26]. For this purpose, the meta-analysis was repeated, omitting one study at a time. Finally, funnel plots were constructed and the Egger regression test ($p_{Egger} < 0.1$) was applied to evaluate small-study effects such as publication bias [27–29]. Stata version 14.1 (Stata Corp, College Station, TX, USA) was used for statistical analyses with user-written commands; $p < 0.05$ was considered significant [30].

Results

The flow diagram in Fig. 1 depicts the results of the literature search and the study selection process. We retrieved 4,905 records published before November 2018: 1,109 from PubMed, 1,200 from Embase, 1,480 from Web of Science, 1,116 from Scopus, and 20 from reference lists in retrieved studies. After eliminating duplicate records, 2,353 potentially eligible studies were identified. After screening the titles and abstracts, 109 studies were selected, of which 27 did not meet all inclusion criteria, leaving a final sample of 82 studies [6,8–12,31–106]. Table 1 summarizes their main characteristics, and Table S2 (Appendix, pp 4–6) exhibits the characteristics and variables gathered by each study. The 82 studies included 26,742 patients: 25,848 with OLPs, 635 with OLL, 150 with LRs, and 109 with dysplastic OLPs; 375 of the patients developed a total of 422 OSCCs.

According to our qualitative analysis with the QUIPS tool, not all

Table 1
Summarized characteristics of reviewed studies.

Total	82 studies
Year of publication	1929–2018
Number of patients	
Total	26,742
Developing oral cancer	375
Number of tumors	422
Sample size, range	17–2119 patients
Diagnostic entity	
Oral lichen planus	78 studies (25,848 patients)
Oral lichenoid lesions	4 studies (635 patients)
Lichenoid reactions	3 studies (150 patients)
Dysplastic oral lichen planus	3 studies (109 patients)
Study design	
Retrospective longitudinal	74 studies
Prospective longitudinal	8 studies
Geographical region	
Europe	42 studies (18 countries)
Asia	21 studies (10 countries)
North America	13 studies (2 countries)
South America	3 studies (2 countries)
Africa	2 studies (1 country)
Oceania	1 study (1 country)
Total	6 continents, 34 countries

Table S2 (Appendix, pp 4–6) summarizes the characteristics of each study.

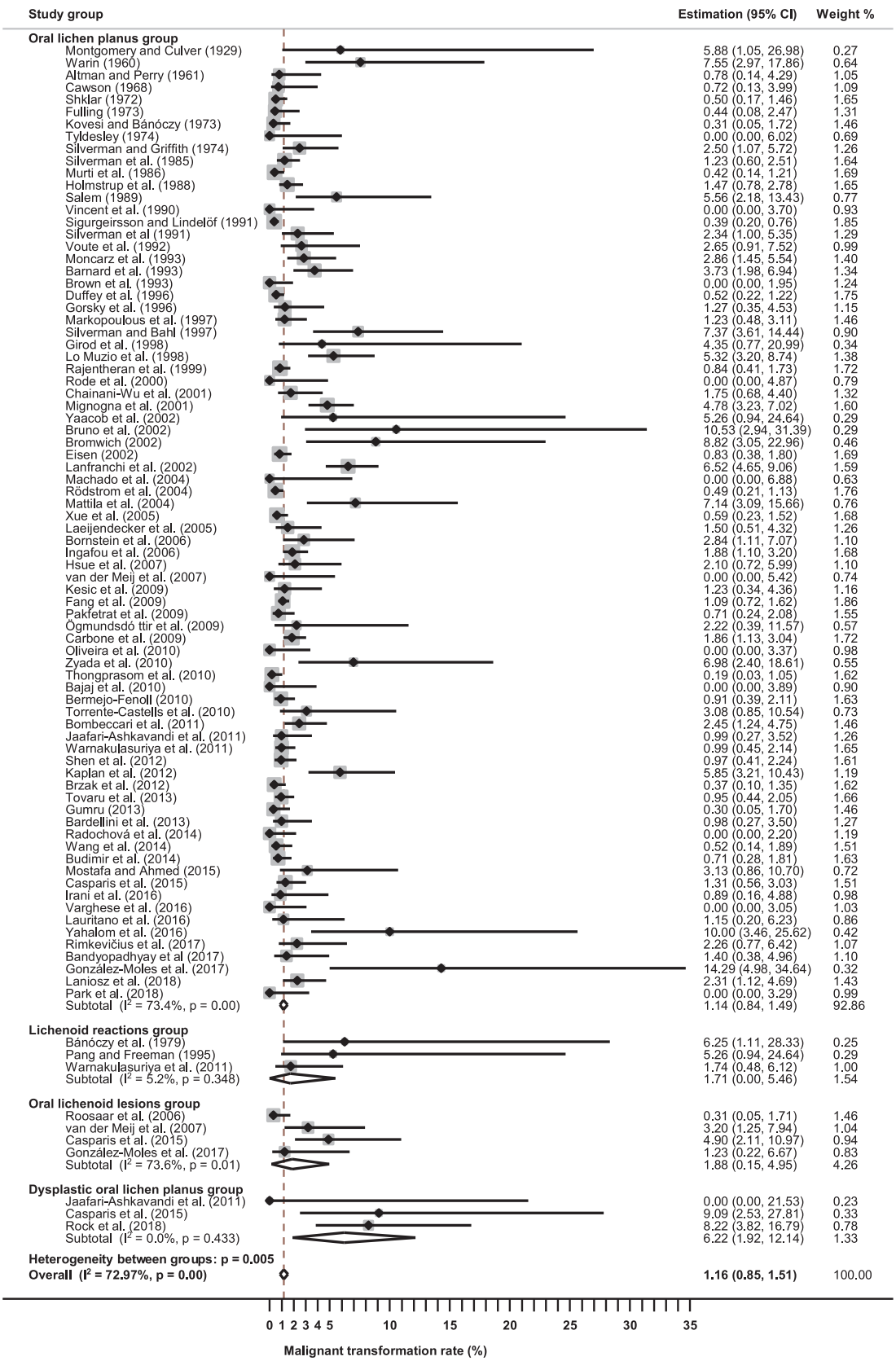

Fig. 2. Forest plot that graphically represents the meta-analysis of the malignant transformation rate stratified by studies that included OLP, OLLs, LRs, and OLP with epithelial dysplasia.

Table 2
Secondary meta-analyses. Malignant transformation rate by subgroup and related risk variables.

				Pooled data		Heterogeneity			Appendix[a]
Analyses	No. of studies	No. of patients	Stat. Model	ES (95% CI)	*P-value*	*Q*	P_{het}	I^2 (%)	
Diagnosis[b]					0.001[c]				Fig. S2, p11
OLP	78	25,848	R	PP = 1.14% (0.84–1.49)		290.0	< 0.001	73.45	
Dysplastic OLP	3	109	R	PP = 6.22% (1.92–12.14)		1.68	0.43	0.0	
Diagnosis[b]					0.561[c]				Fig. S3, p12
OLP	78	25,848	R	PP = 1.14% (0.84–1.49)		290.0	< 0.001	73.45	
OLL	4	635	R	PP = 1.88% (0.15–4.95)		11.36	0.01	73.6	
Diagnosis[b]					0.195[c]				Fig. S4, p13
OLP	78	25,848	R	PP = 1.14% (0.84–1.49)		290.0	< 0.001	73.45	
LR	3	150	R	PP = 1.71% (0.00–5.46)		2.11	0.348	5.25	
Diagnostic criteria[b]					< 0.001[c]				Fig. S5, p14
Clinical and histopathological	55	17,691	R	PP = 1.61% (1.18–2.09)		205.18	< 0.001	73.68	
Clinical or non-exhaustive	27	9051	R	PP = 0.42% (0.16–0.77)		57.82	< 0.001	55.03	
Minimum follow up[b]					0.063[c]				Fig. S6, p15
≥6 months	29	8896	R	PP = 1.65% (1.06–2.35)		107.21	< 0.001	73.88	
< 6 months	53	17,846	R	PP = 0.97% (0.63–1.38)		196.54	< 0.001	73.54	
Minimum follow up[b]					0.048[c]				Fig. S7, p16
≥12 months	16	3966	R	PP = 2.16% (0.91–3.79)		89.10	< 0.001	83.17	
< 12 months	66	22,776	R	PP = 1.09% (0.79–1.42)		218.91	< 0.001	70.31	
Sex[e]									
Male *vs.* Female	48	20,737	F	RR = 1.23 (0.98–1.54)	0.073	39.49	0.774	0.0	Fig. S8, p17
Age[e]									
Older *vs.* younger	10	2244	F	RR = 1.09 (0.51–2.32)	0.827	4.58	0.869	0.0	Fig. S10, p19
Smoking[e]									
Smokers *vs.* non-smokers	19	5918	F	RR = 1.98 (1.28–3.05)	0.002	16.65	0.478	0.0	Fig. S11, p20
Alcohol[e]									
Drinkers *vs.* non-drinkers	8	2719	F	RR = 2.28 (1.14–4.56)	0.019	9.53	0.217	26.5	Fig. S12, p21
HCV[e]									
HCV-positive *vs.* -negative	6	2160	R	RR = 4.46 (0.98–20.22)	0.053	17.17	0.004	70.9	Fig. S13, p22
Geographical region[b]					0.09[c]				Fig. S14, p23
Africa	2	107	R	PP = 4.47% (1.07–9.53)		0.00	0.990	0.0	
Asia	21	7371	R	PP = 0.80% (0.39–1.31)		55.21	< 0.001	63.77	
Europe	42	14,209	R	PP = 1.26% (0.84–1.76)		150.29	< 0.001	72.72	
North America	13	4383	R	PP = 1.31% (0.64–2.16)		44.00	< 0.001	72.73	
South America	3	653	R	PP = 1.28% (0.00–7.91)		20.74	< 0.001	90.36	
Oceania	1	19	—	PP = 5.26% (0.94–24.64)		—	—	—	
Localization									
Tongue *vs.* others[e]	19	10,291	F	RR = 1.82 (1.21–2.74)	0.004	11.29	0.882	0.0	Fig. S16, p25
Clinical aspect									
Atrophic[d]	20	810	R	PP = 0.02% (0.00–0.85)	N/A	24.92	0.16	23.77	Fig. S17, p26
Bullous[d]	11	68	R	PP = 0.00% (0.00–0.05)	N/A	1.83	0.997	0.0	Fig. S18, p27
Erosive[d]	27	2120	R	PP = 1.87% (1.05–2.85)	N/A	34.72	0.118	25.12	Fig. S19, p28
Papular[d]	8	39	R	PP = 0.00% (0.00–10.03)	N/A	8.93	0.258	21.61	Fig. S20, p29
Plaque[d]	9	164	R	PP = 0.00% (0.00–0.45)	N/A	4.48	0.811	0.0	Fig. S21, p30
Reticular[d]	24	2596	R	PP = 0.00% (0.00–0.00)	N/A	19.43	0.676	0.0	Fig. S22, p31
Red[d]	40	5278	R	PP = 1.88% (1.17–2.71)	N/A	97.19	< 0.001	59.87	Fig. S23, p32
White[d]	40	5637	R	PP = 0.03% (0.00–0.22)	N/A	57.09	0.031	31.68	Fig. S24, p33
Atrophic-erosive *vs.* reticular[e]	20	4919	F	RR = 4.09 (2.40–6.98)	< 0.001	13.74	0.798	0.0	Fig. S25, p34
Red *vs.* White[e]	39	10,759	F	RR = 2.80 (2.05–3.84)	< 0.001	21.94	0.929	0.0	Fig. S26, p35
Overall risk of bias[b]					0.002[c]				Fig. S27, p36
High	47	15,540	R	PP = 0.61% (0.34–0.93)		114.94	< 0.001	59.98	
Low	35	11,202	R	PP = 1.91% (1.35–2.56)		150.64	< 0.001	77.43	

Abbreviations: Stat., statistical; F, fixed-effects model; R, random-effects model; ES, estimation; CI, confidence intervals; OLP, oral lichen planus; OLL, oral lichenoid lesions; LR, lichenoid reactions; PP, pooled proportion; RR, relative risk.

[a] More information in the Appendix.
[b] Proportion meta-analyses (Subgroup analyses).
[c] Test for between-subgroup differences.
[d] Proportion meta-analyses.
[e] Prognosis meta-analyses.

studies were conducted with the same rigor; the domains showing greatest potential risk of bias were study confounding and statistical analysis/reporting. The quality of some studies was also sub-optimal in the remaining four domains (Fig. S1, Table S3, Appendix pp7–10).

In the main meta-analysis, the combined malignant transformation rate was 1.16% (95% CI = 0.85–1.51), as shown in Fig. 2. A moderate degree of heterogeneity was found according to the Higgins cutoff point (I^2 = 72.97%) (p < 0.001), with a malignant transformation rate of 1.14% (95% CI = 0.84–1.49) for the OLP group, 1.88% [95% CI = 0.15–4.95] for the OLL group, and 1.71% [95% CI = 0.00–5.46] for the LR group. There was no significant difference between the OLL or LR group and the OLP group (p = 0.561 and p = 0.195, respectively, as shown in Table 2 and Figs. S3 and S4 (Appendix pp 12, 13). Malignant transformation was recorded in 6.22% (95% CI = 1.92–12.14) of the dysplastic OLP group, a significantly higher percentage than observed in the OLP group (p < 0.001; Table 2, Fig. S2, Appendix

p11).

In the sensitivity analysis, our stepwise procedure showed that the combined estimations do not depend on the influence of any individual study (Table S4, Appendix p38). However, a small-study effect was revealed by the funnel plot asymmetry and the statistical test results ($p_{Egger} < 0.001$) (Fig. S28, Appendix p.37); therefore, it is not possible to rule out publication bias, among other potential sources of bias.

Table 2 exhibits the results of secondary analyses of the malignant transformation rate in different subgroups to identify potential sources of heterogeneity and to explore possible predictive factors for malignization. The highest malignant transformation rate was observed in studies that based the diagnosis of OLP or LR on strict clinical and histopathological criteria, and the difference with the remaining studies was statistically significant (1.61%, 95% CI = 1.18–2.09 *vs*. 0.42%, 95% CI = 0.16–0.77, p < 0.001; Table 2, Fig. S5, Appendix p14). The malignant transformation rate was also higher in studies with a longer follow-up period, with a difference that was close-to-significant when the follow-up was at least 6 months (1.65%, 95% CI = 1.06–3.35, p = 0.06; Table 2, Fig. S6, Appendix p15) and significant when it was 12 months (2.16%, 95% CI = 0.91–3.79, p = 0.048; Table 2, Fig. S7, Appendix p16). A higher risk of oral cancer was found for males *versus* females, although this difference was only close-to-significant (RR = 1.23, 95% CI = 0.98–1.54, p = 0.073; Table 2, Fig. S8, p17), while no association was found between cancer risk and patient age (p = 0.827; Table 2, Figs. S9, S10, Appendix pp18, 19). In the study of oral cancer risk factors, tobacco and alcohol consumption was associated with a significantly higher risk in OLP patients (RR = 1.98, 95% CI = 1.28–3.05, p = 0.002, and RR = 2.28, 95% CI = 1.14–4.56, p = 0.02, respectively), and hepatitis C virus (HCV)-positivity with close-to-significant increase in their risk (RR = 4.46, 95% CI = 0.98–20.22, p = 0.053) in OLP patients (Table 2, Figs. S11–S13, Appendix pp20–22). The malignant transformation rate did not significantly vary among geographical regions (p = 0.09; Fig. 3, Table 2, Fig. S14, Appendix p23). The risk of cancer development was significantly higher on the tongue (32.70%; Fig. S15 Appendix p24) than on any other site in the oral cavity (RR = 1.82, 95% CI = 1.21–2.74, p = 0.004; Table 2, Fig. S16, p25). The highest malignant transformation rate was observed in red lesions (1.88%, 95% CI = 1.17–2.71, Table 2, Fig. S17–S24, appendix pp26–33), and the meta-analysis of reticular white lesions suggests that there is no risk of their malignization (Table 2, Fig. S22, Appendix p31). Subsequent meta-analyses comparing red with white lesions and atrophic-erosive lesions with reticular lesions revealed major and significant differences (RR = 2.80, 95% CI = 2.05–3.84, p < 0.001 and RR = 4.09, 95% CI = 2.40–6.98, p < 0.001, respectively; Table 2, Figs. S25, S26, Appendix pp34, 35). Finally, the meta-analysis stratified by study quality showed that the malignant transformation rate was considerably and significantly lower in those with higher risk of potential bias (0.61%, 95% CI = 0.34–0.93 *vs*. 1.91%, 95% CI = 1.35–2.56, p = 0.002; Table 2, Fig. S27, Appendix p36).

Discussion

This systematic review and meta-analysis of 82 studies and 26,742 patients reveals reported malignant transformation rates of 1.14% for OLP, 1.88% for OLLs and 1.71% for LRs. An important conclusion of our study was that their potential for malignant transformation is likely underestimated in the literature, with most authors considering OLP, OLLs and LRs as low-risk OPMDs [107]. This may lead to their inadequate surveillance, and the resulting delay in the diagnosis of oral carcinomas arising on these lesions may have negative implications for survival, treatment cost, and post-treatment quality of life.

The restrictive diagnostic criteria [5] for OLP applied by many researchers may be responsible for the underestimation of its malignant potential. Notably, studies that considered epithelial dysplasia as an exclusion criterion [5,108] have reported a markedly and significantly lower malignant transformation rate (1.14%, 95% CI = 0.84–1.49) than published by studies that did not (6.22%, 95% CI = 1.92–12.14) (p = 0.001). Epithelial dysplasia provides histological evidence of progress towards malignant transformation of the oral epithelium and is considered the gold standard for assessing the risk of an OPMD [7]. Therefore, the exclusion from studies of OLPs with epithelial dysplasia would lead to the selection of cases with lower malignization risk. In this regard, Van der Meij et al. [5,6] attributed malignant potential exclusively to lesions that they designated as OLLs because they did not meet their strict clinicopathological criteria for a diagnosis of OLP. However, we found no difference (P = 0.561) in malignant transformation rate between OLLs (1.88%, 95% CI = 0.15–4.95) and OLPs defined according to Van de Meij and colleagues [5,6] (1.14%, 95% CI = 0.84–1.49); therefore, in our view, OLLs and OLP cannot be considered as distinct diagnostic entities with respect to their malignization risk. Our meta-analysis also demonstrate that oral LRs, which resemble OLP and are induced by drugs or contact with dental restorative materials, also have malignant transformation potential (1.71%, 95% CI = 0.00–5.46). In fact, we found no significant difference in transformation rate between LRs and OLP (1.14%, 95% CI = 0.84–1.49) (p = 0.195). Accordingly, we conclude that OLP, OLLs and oral LRs should all be considered with any doubt, potentially malignant and they should be biopsied to determine the presence and severity of dysplasia. This proposal is supported by the results of our meta-analysis, which revealed significantly higher (p < 0.001) malignant transformation rates in studies that applied both clinical and histopathological diagnostic criteria (1.61%, 95% CI = 1.18–2.09) than in those using clinical criteria alone (0.42%; 95% CI = 0.16–0.77).

Besides possibly over-strict diagnostic criteria, underestimation of the malignant transformation rate of these lesions may also result from the inadequate follow-up of patients, with a significantly higher rate (p = 0.048) being recorded when this was properly conducted for at least 12 months (1.09%, 95% CI = 0.79–1.42 *versus* 2.16%, 95% CI = 0.91–3.79). Patients with oral lesions that may malignize at any time should evidently be followed up over an extensive period, even for life, although there is a lack of information to support recommendations on the appropriate periodicity of follow-up sessions. We recently reported that a high percentage of patients with OLP and OLLs do not comply with their follow-up schedule despite being clearly informed of the potentially malignant nature of their lesions, suggesting the need to establish recall programs for these patients [8].

Our meta-analysis identified clinical factors and habits that influence the risk of malignization. Thus, oral cancer more frequently developed in patients who smoked (RR = 1.98, 95% CI = 1.28–3.05, p = 0.002) and consumed alcohol (RR = 2.28, 95% CI = 1.14–4.56, p = 0.019) than in those who did not. Smoking and alcohol consumption have been exclusion criteria in some studies of OLP malignant transformation as confounding factors [3,109]. However, we do not support this approach because research on the etiology of oral cancer suggests that these behaviors may potentiate the malignant transformation risk of OLP, OLLs or LR in individual patients [3,110], and there could be a summative oncogenic effect (tobacco and/or alcohol plus OLP, OLLs or LRs) as reported for other OPMDs (e.g., leukoplakia) [110]. In this regard, there is an evident need to persuade patients with OLP, OLLs and LRs to quit tobacco and alcohol consumption. Another risk factor for OLP malignization to emerge in this meta-analysis was the presence of HCV infection (RR = 4.46, 95% CI = 0.98–20.22, p = 0.053). The association of OLP and HCV infection is not infrequent, with HCV infection being reported in up to 20% of OLP cases [111]. These findings support the inclusion of HCV serology in the clinical protocol for OLP management. The reasons for the increased cancer risk in HCV-infected OLP patients remains unknown, although HCV infection *per se* is known to increase the risk of oral cancer [112] and may behave as a potentiating factor, as in the case of tobacco and alcohol [113]. Our review found also that OLP can malignize at any age, and there was no significant difference in the frequency of transformation

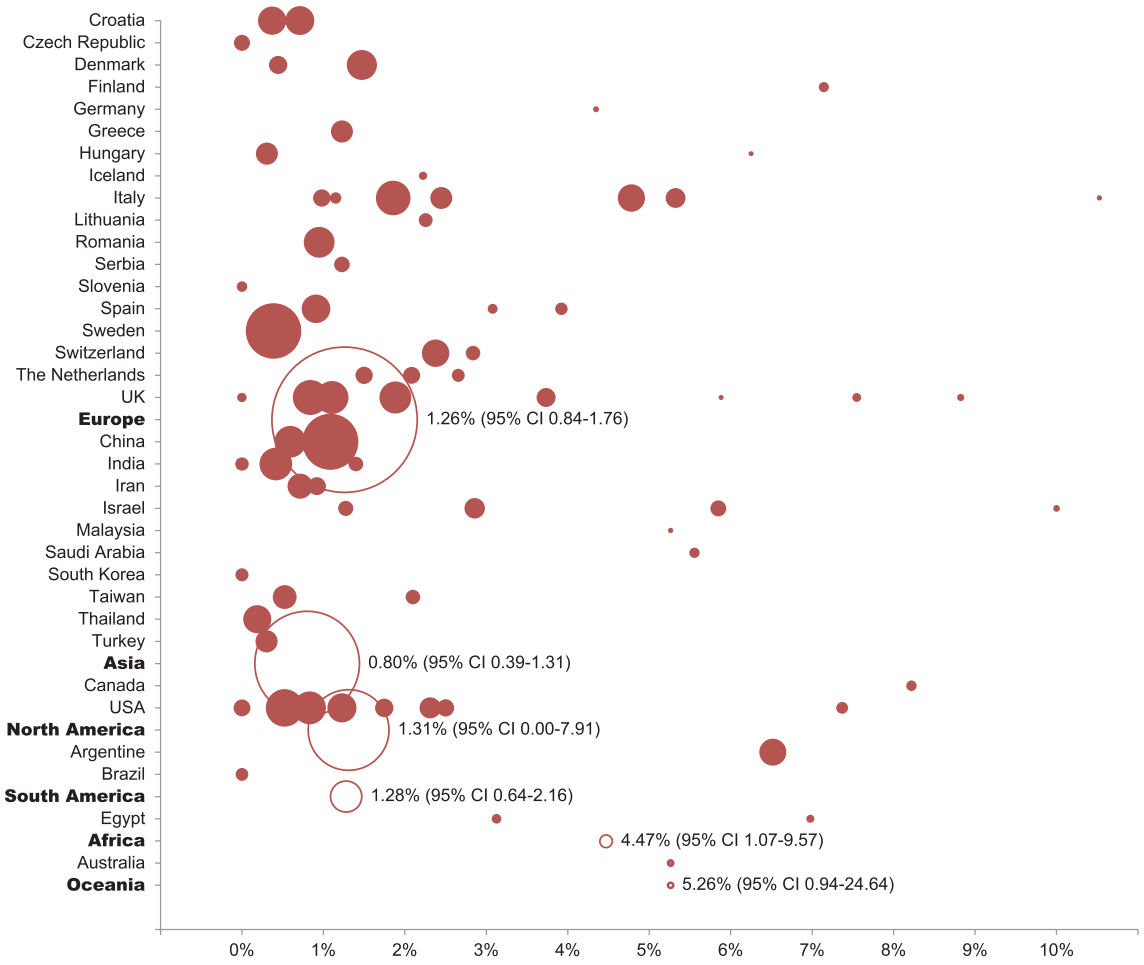

Fig. 3. Bubble chart graphically representing the malignant transformation rate of OLP, OLLs or LRs by country and geographical region. Filled bubbles correspond to the individual studies performed in each country. The order of bubbles on the x axis represents the malignant transformation rate of OLP, OLLs or LRs. Empty bubbles correspond to meta-analyzed estimations by geographical region. The bubble diameter is proportional to the sample size.

between patients aged under and over 40 years (RR = 1.09, 95% CI = 0.51–2.32, p = 0.827). Moreover, there appears to be no differences among the continents in which studies take place (p = 0.09).

An important finding of our meta-analysis was that increased malignant transformation risk is exclusively associated with lesions that are erosive and/or atrophic (RR = 4.09, 95% CI = 2.40–6.98, p < 0.001), whereas exclusively reticular lichens showed no risk in meta-analytical terms. Hence, follow-up efforts should focus on atrophic-erosive (red) lesions rather than exclusively reticular (white) lesions. With regard to the localization of lesions, the tongue was found to carry a significantly higher risk of malignant transformation in comparison to other oral sites (RR = 1.82, 95% CI = 1.21–2.74, p = 0.004) and was the most frequent area affected by cancer in OLP/OLLs (138/422; 32.70%). Consequently, atrophic-erosive lesions on the tongue are of particular concern.

Finally, according to our qualitative evaluation using the QUIPS tool, not all studies in our meta-analysis were conducted with the same rigor. The highest risk of potential bias was in the domains "study confounding" and "statistical analysis and reporting". A lower quality of study proved to be a factor potentially contributing to an underestimation of malignant transformation rates, which were much higher in studies that met our quality criteria, as listed in Table S3 of the appendix (1.91%, 95% CI = 1.35–2.56, p = 0.002), than in studies of lower quality (0.61%, 95% CI = 0.34–0.93).

Some potential limitations of our study are frequently encountered in meta-analyses. First, we only selected studies in the English language, which may imply a loss of information only available in other languages. However, we addressed this possible drawback by examining articles published in other languages in the CNKI and LILACS databases, as recommended [114,115], finding a high proportion of papers duplicated in English-language journals. Second, there were limitations in the amount of data available for many of our secondary analyses (e.g., on treatment variables, multiple tumor development, and time interval before malignant transformation, among others). Third, our meta-analysis revealed heterogeneity in the global OLP malignant transformation rate (p < 0.001, I^2 = 72.97%), a frequent finding in meta-analyses of proportions [116]. In order to overcome this limitation, we applied a random-effect statistical model in all proportion meta-analyses and conducted secondary stratified analyses of more homogeneous subgroups of studies. Finally, the funnel plot was significantly skewed to the right (p_{Egger} < 0.001); this is likely attributable to small-study effects, which are common in the health science literature because of the bias towards publishing positive results [117]. Despite the above limitations, the robust nature of our meta-analysis is indicated by the forest plots -which demonstrate strong statistical associations between OLP and LR malignant transformation and numerous study variables- and by the sensitivity analysis.

In conclusion, our systematic review and meta-analysis present consistent results and contribute evidence of an underestimation of the malignant transformation rate for OLPs, OLLs and LRs, currently reported to be 1.14%, 1.88% and 1.71%, respectively. Major reasons for this trend would be the application of restrictive diagnostic criteria, especially the exclusion of OLP cases with epithelial dysplasia, as well as inadequate follow-up periods and the low quality of some studies.

The risk of malignant transformation was found to be increased by localization on the tongue, the presence of erosive and/or atrophic areas, the consumption of tobacco and/or alcohol, and infection with HCV.

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Declaration of Competing Interest

None declared

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.07.012.

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