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Systematic Review

Malignant Transformation of Oral Lichen Planus—An Umbrella Study of Systematic Reviews

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Abstract: Oral lichen planus (OLP) is classified as a potentially malignant disorder. Systematic reviews collating longitudinal observation studies provide evidence of the rate or proportion of malignant transformation. We conducted an umbrella study of published systematic reviews. An extensive English-language study search was carried out in several databases to identify relevant articles, providing systematic reviews on the malignant transformation of OLP. Data from eight systematic reviews published between 2014 and 2023 are presented. The reported proportions of malignant transformation ranged from 1.1% to 1.4%. A meta-analysis based on the 10 highest-quality studies yielded a higher proportion of malignant transformation (2.28%). We list some limitations found in several of these systematic reviews. Some studies reported an increased risk of malignancy in OLP lesions, demonstrating epithelial dysplasia. In view of the consistent evidence of the risk of oral malignancy, OLP patients should be monitored carefully to detect early cancer development.

Keywords: lichen planus; oral cancer; malignant transformation; epithelial dysplasia; evidence-based medicine

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1. Introduction

Oral lichen planus (OLP) "is a chronic inflammatory disease, characterized by a T-cell mediated response against epithelial cells with a band-like infiltrate of T-cells leading to apoptosis and destruction of basal cells". The first detailed clinical description of OLP, in which nine different subtypes were identified and classified into two groups—non-erosive-white forms (linear, reticular, annular, papular, and plaque-like) and erosive/atrophic forms (erythematous, erosive, ulcerative, and bullous)—was presented by BED Cooke in the *British Dental Journal* [1]. While, in most patients affected by OLP, the disease remains asymptomatic, a small number of patients experience oral soreness due to erythema and ulceration. Oral soreness experienced by patients with OLP may result in the withdrawal of oral hygiene procedures, which may predispose them to the development of periodontal disease [2] and dental caries. The most significant clinical problem with OLP is its potential to transform into malignancy. The first case report of a French patient diagnosed with OLP that transformed to cancer was published in 1910 by Hallopeau [3]. Since then, based on longitudinal follow-up studies, several case series and cohort studies (both prospective and retrospective) have appeared in the literature, describing the malignant transformation (MT) rates of OLP. Based on this evidence, which at the time had not been systematically analyzed, in 2005, the WHO Collaborating Centre for Oral Cancer included OLP in their classification of oral potentially malignant disorders [4]. Between 2007 and 2020, several systematic reviews and meta-analyses critically examining the evidence on MT were published. Based on this evidence, in 2020, an update on the nomenclature and classification by the WHO Collaborating Centre included OLP and, for the first time, oral lichenoid lesions (OLLs) as

potentially malignant disorders [5]. Following this expert workshop, a systematic review of systematic reviews was also undertaken by the same group [6].

In order to provide the reader with the evidence accumulated from several systematic reviews, the aim of this umbrella review is to provide a synthesis of existing systematic reviews and to update the knowledge on the MT of OLP.

2. Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-based guidelines specifically designed for systematic reviews of systematic reviews published in *Umbrella Reviews Evidence Synthesis with Overviews of Reviews and Meta-Epidemiologic Studies* [7].

2.1. Protocol

We registered a protocol in *PROSPERO, the International Prospective Register of Systematic Reviews* (CRD42019128539; www.crd.york.ac.uk/PROSPERO, accessed on 1 May 2023), for a previous systematic review of systematic reviews [6], whose methodology was also applicable to the present study. The protocol also adhered to PRISMA-P reporting guidelines in order to ensure a rigorous approach [8].

2.2. Search Strategy

An extensive search was carried out in the Embase, Web of Science, Scopus and MEDLINE databases (via PubMed) (U.S. National Library of Medicine; https://www.ncbi.nlm.nih.gov/pubmed/, accessed on 1 May 2023), without lower date limitations. Additionally, included in this review is information obtained from ancestry searches, which extracted citations from articles that were not retrieved during our initial searches. The searches were designed by combining specific thesaurus terms (i.e., MeSH and EMTREE) with free terms, built to maximize sensitivity (the keywords and syntax used to search each database can be found in Appendix A).

2.3. Eligibility Criteria

The *Condition, Context and Population (CoCoPop) question* [9] was designed in order to identify systematic reviews, with or without meta-analysis (*study design*), assessing malignant transformation (*condition*) in OLP/OLL patients (*population*). No restrictions (*context*) were applied in relation to diagnostic criteria, the lengthening of follow-up periods, the study design included in the systematic reviews, or geographical areas. Only English-language publications in peer-reviewed journals were included; meeting abstracts and dissertations were excluded. The eligibility criteria were independently applied by all authors (SW, PRG, and MAGM). The articles were selected in two phases: first, titles and abstracts were screened to select articles that apparently met the inclusion criteria; then, the full texts of the selected articles were read, and those that failed to meet the eligibility criteria were excluded. The evaluators exhibited excellent calibration in the process of identifying and selecting studies, benefiting from prior research training [6]. The level of agreement among the evaluators regarding study eligibility was measured using Cohen's kappa statistic, resulting in a perfect consensus without any discrepancies (100% inter-agreement, κ-value = 1.00).

2.4. Data Extraction

Three authors (SW, PRG, and MAGM) collected data from the included systematic reviews. The process of data extraction involved the completion of a standardized data collection form using Microsoft Excel (version 16). Furthermore, the datasets underwent multiple rounds of cross-checking, with any discrepancies resolved through a consensus-based approach. Data on the first author, publication year, sample size (number of included primary-level studies), number of patients with OLP/OLL, proportion of cases of malignant transformation, pooled proportions derived from meta-analytical techniques, risk of

malignancy in OLP lesions demonstrating epithelial dysplasia, and methodological study limitations were extracted.

2.5. Evaluation of Quality and Risk of Bias of Systematic Reviews

Three authors (SW, PRG, and MAGM) used the "*A MeaSurement Tool to Assess systematic Reviews*" *AMSTAR2* checklist [10], a specific scale designed to critically appraise systematic reviews through the following 16 items. 1. Did the research questions and inclusion criteria for the review include the components of PICO? 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? 3. Did the review authors explain their selection of the study designs for inclusion in the review? 4. Did the review authors use a comprehensive study search strategy? 5. Did the review authors perform study selection in duplicate? 6. Did the review authors perform data extraction in duplicate? 7. Did the review authors provide a list of excluded studies and justify the exclusions? 8. Did the review authors describe the included studies in adequate detail? 9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review? 10. Did the review authors report on the sources of funding for the studies included in the review? 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? 12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis? 13. Did the review authors account for risk of bias in individual studies when interpreting/discussing the results of the review? 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? Following strict guidelines, items 2, 4, 7, 9, 11, 13, and 15 were judged as critical domains, and the rest as non-critical domains. The overall confidence was categorized as "High" (no or one non-critical weakness), "Moderate" (more than one non-critical weakness), "Low" (one critical flaw with or without non-critical weaknesses), and "Critically low" (more than one critical flaw with or without non-critical weaknesses). Furthermore, an overall score (over 16 points) was also calculated by summing up all judged items. Two independent AMSTAR2 scores were first recorded (i.e., SW and PRG-MAGM) in a standardized manner using Microsoft Word (version 16). Subsequently, the discrepancies were resolved jointly by consensus.

2.6. Evidence Synthesis

Once the risk of bias was formally evaluated, the main results and limitations drawn from the included secondary-level systematic reviews were critically described by narrative synthesis methods. Canonical meta-analytical techniques are not applicable to this type of design and were not a priori considered in our study protocol.

3. Results

In our search on MT of OLP, eight systematic reviews were found in the published literature from 2014 to 2023 (Figure 1).

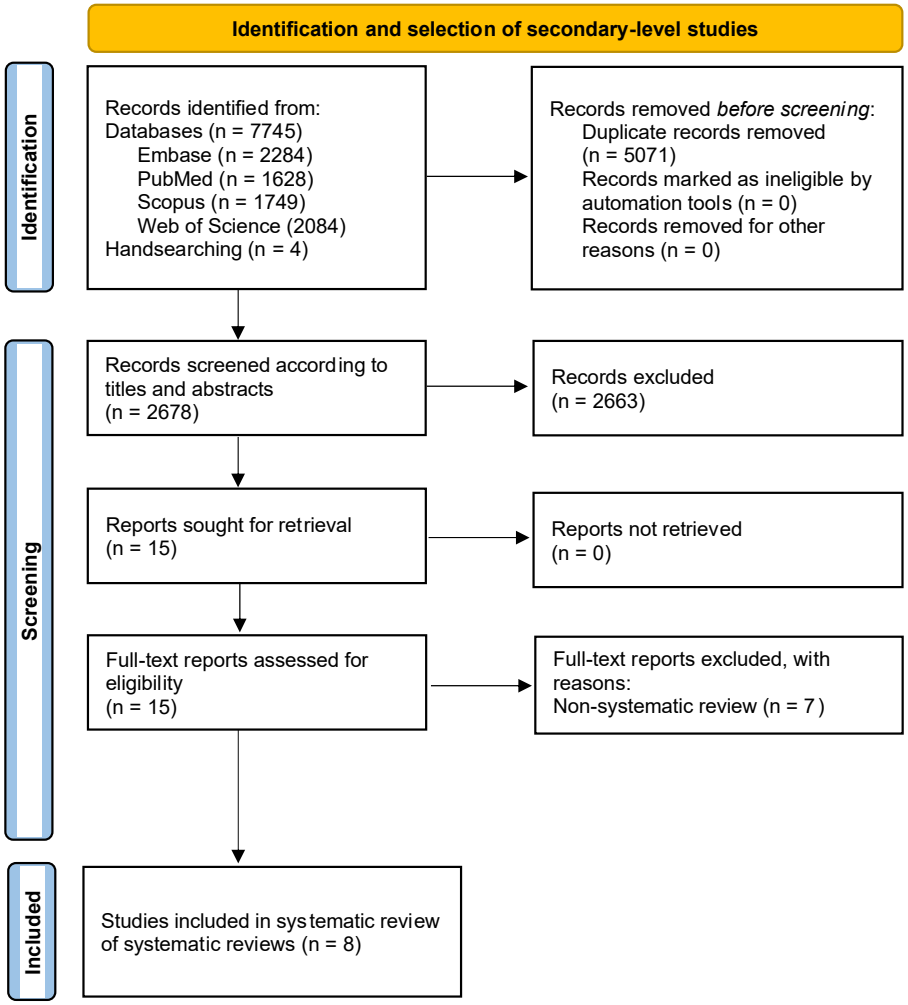

Figure 1. PRISMA flow diagram of the identification and selection of systematic reviews addressing the malignant transformation risk of OLP.

According to the evaluation of quality and risk of bias using *A MeaSurement Tool to Assess systematic Reviews* AMSTAR2 tool, not all systematic reviews were designed, conducted, and/or reported with the same rigor (Figure 2). Most critical items in general were judged as having a high risk of potential bias across systematic reviews. The critical domains were generally judged to be at high risk of potential bias for most of the systematic reviews.

Study (year)	Study Design	AMSTAR2 tool. Items for potential risk of bias assessment.																(*) Critical weaknesses	Overall rating (based on critical weaknesses)	Total Score
		1	* 2	3	* 4	5	6	* 7	8	* 9	10	* 11	12	* 13	14	* 15	16			
Fitzpatrick et al. (2014)	SR																	1/7	LOW QUALITY	9/13
Aghbari et al. (2017)	SR+MA																	4/7	CRITICALLY LOW QUALITY	7/16
Giuliani et al. (2018)	SR+MA																	3.5/7	CRITICALLY LOW QUALITY	8.5/16
González-Moles et al. (2019)	SR+MA																	0.5/7	HIGH QUALITY	14.5/16
Iocca et al. 2019	SR+MA																	3,5/7	CRITICALLY LOW QUALITY	7.5/16
Idrees et al. 2020	SR+MA																	4/7	CRITICALLY LOW QUALITY	8/16
González-Moles et al. (2021)	SR+MA																	0/7	HIGH QUALITY	15/16
Li *et al.* 2023	SR+MA																	6.5/7	CRITICALLY LOW QUALITY	5.5/16

Legend: (*), critical weakness item; green, yes (low potential risk of bias); yellow, partial (moderate); red, no (high); blue, not applicable for systematic reviews without meta-analysis.
Abbreviations: AMSTAR, A MeaSurement Tool to Assess systematic Reviews; SR, systematic review; MA, meta-analysis.

Figure 2. Quality plot graphically representing the risk of bias across systematic reviews and meta-analyses addressing the malignant transformation risk of OLP, assessed using AMSTAR2 tool. The items were depicted as red (High risk of bias), yellow (partial/moderate risk of bias), green (low risk of bias), or blue (not applicable) [6–13].

A Summary Systematic Reviews

The systematic review by Fitzpatrick et al. [11] was the first attempt to systematically evaluate the evidence regarding MT of OLP. The authors searched three databases—PubMed, Embase, and Thomson Reuters Web of Science—and collated observational studies involving human subjects published in the English language in peer-reviewed journals. Selected studies were limited to cohort studies (prospective or retrospective) and large case series or reviews that provided sufficient information. Inclusion criteria included patients who had a pathology confirmed diagnosis of OLP or OLL at the time of initial presentation. Patients who had dysplasia on initial biopsy were excluded from the OLP group. A modified Newcastle-Ottawa Scale was used for quality assessment for risk of bias of the selected studies. The review reported on clinical descriptors, the frequency, and time to transformation. Sixteen studies were considered eligible for inclusion. Of 7806 patients diagnosed with OLP, 85 later developed OSCC and five cases of carcinoma in situ. Of 125 patients diagnosed with OLL, four developed OSCC. The proportion of transformation for OLP was 1.09 percent (range 0 to 3.5 percent) and 1.14 percent when cases of carcinoma in situ were added to the cases of SCC; and among OLL cases, 3.2 percent transformed. Patients' mean age when OSCC developed was 60.8 years. A slight predominance of female patients was noted among cases with MT. OLP of the tongue had a higher predisposition for malignant transformation. The mean time taken for malignant transformation was 51.4 months. The authors acknowledged that excluding cases with dysplasia on initial biopsy may have resulted in under estimation of malignant transformation of OLP.

Aghbari et al. [12] performed a systematic review and meta-analysis to estimate the malignant potential of OLP and OLL and determinants associated with MT. They searched Medline (through PubMed), Scopus, and Web of Knowledge, and they used MOOSE guidelines for their meta-analysis. An amount of 57 studies were included in the review. Data covered 19,676 OLP and 419 OLL patients. In this large cohort, 280 patients developed OSCC. The proportion of malignant transformations among OLP patients ranged from 0.3% to 14.3% in individual studies. Using the random effects model and the Der-Simonian Liard method, the authors calculated an overall pooled proportion (PP) of MT of 1.1% [95% CI: 0.9–1.4%]. In a subgroup analysis using van der Meij criteria (2003), the PP was 0.9% (95% CI 0.5% to 1.3%). In four studies based on 419 OLL patients in whom 13 developed malignancies, the rate of transformation was estimated at 2.5% [95% CI: 1–4%]. The range reported in individual datasets was between 1.2% and 4.9%. The review provided MT rates of OLP by clinical type: erosive OLP (1.7%), atrophic OLP (1.3%), and the reticular type, with a much lower rate (0.1%). Males had higher MT rates than females (OR = 1.11; [95% CI: 0.83, 1.48; p = 0.48), and smokers (in thirteen studies) and alcoholics (in five studies) had a significantly higher rates of MT compared to non-smokers and non-alcohol users (OR = 2, 95% CI [1.25, 3.22; p = 0.004) and (OR = 3.52, 95% CI [1.54, 8.03], p = 0.003), respectively. In reports from two studies (561 OLP cases), a higher prevalence of malignancy among Hepatitis C Virus (HCV) + ve patients was noted in comparison to the HCV -ve patients (OR = 5, 95% CI [1.56,16.07], p = 0.007). Diabetes had no association with malignancy among OLP cases (OR = 1.49, 95% CI [0.48, 4.62], p = 0.49). Based on their findings, the authors recommended regular follow-up for OLP and OLL patients.

Giuliani et al. [13] performed a systematic review of the published literature using the Prisma protocol to determine the MT rate of OLP and to inquire whether OLL has a higher or lower MT rate compared with OLP. A subgroup analysis was undertaken by age, sex, oral site, and OLP type. PubMed, Scopus, and Web of Science were used as search engines. The quality of the included papers and the risk of bias were assessed using the modified Ottawa scale. Following the searches, they selected 21 articles, 18 being retrospective and three being prospective. Among 6559 patients, 92 OSCC were reported during a mean follow-up time of 83.3 months, amounting to an overall malignant transformation of 1.40% (1.37% for OLP and 2.43% for OLL). The mean age at oral cancer detection was 62.9 years (63.7 females and 62.3 males). In subgroup analysis, they reported a higher

cancer risk in women (57 vs. 28). The tongue was the predominant site at the lateral margins (39 cases), particularly on the lateral sides. Among different clinical types, red or white and red mixed forms developed more cancers (66 vs. 19) compared with white forms. Interestingly, 27 OLP patients who developed cancer had received past systemic and topical steroid therapy for their OLP. The mean time for transformation from OLP detection was 61.9 months.

González-Moles et al. [14] performed a systematic review and meta-analysis to determine the malignant transformation rate of OLP, OLLs, and oral lichenoid reactions (OLRs). They searched PubMed, Embase, Web of Science, and Scopus for studies published until the end of November 2018. Inclusion criteria were met by 82 studies (a total of 26,742 patients, with clinical subgroups consisting of 25,848 OLPs, 635 OLL, and 150 LRs). An amount of 109 were reported to have had epithelial dysplasia in OLP biopsies. In this cohort, 375 cases developed a total of 422 OSCCs. In their meta-analysis, the overall malignant transformation rate was 1.16% (95% CI = 0.85–1.51). Among the clinical subgroups, the OLP group had a malignant transformation rate of 1.14% (95% CI = 0.84–1.49), a slightly higher rate of 1.88% [95% CI = 0.15–4.95] was reported for the OLL group, and an intermediate rate of 1.71% [95% CI = 0.00–5.46] was reported for the LR group. The malignant transformation recorded in the dysplastic OLP group was 6.22% (95% CI = 1.92–12.14), being significantly higher ($p < 0.001$). The authors performed a secondary analysis of different subgroups to explore possible predictive factors for transformation. Higher MT rates were observed in studies that applied strict clinical and histopathological criteria for OLP diagnosis, or when OLP was followed up for a longer period (over one year). The males had a higher risk of oral cancer compared with females (RR = 1.23, 95% CI = 0.98–1.54, $p = 0.073$). The risk of any associated lifestyle habits, current and past tobacco use, and alcohol consumption posed 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). Among the groups with hepatitis C virus (HCV) positivity, their risk (RR = 4.46, 95% CI = 0.98–20.22, $p = 0.053$) was higher, but without statistical significance. The group with OLP on the tongue (32.7%) had higher risk of malignancy than any other site in the oral cavity (RR = 1.82, 95% CI = 1.21–2.74, $p = 0.004$) and in those with red lesions (1.88%, 95% CI = 1.17–2.71). When OLP presentation was confined to reticular white lesions (without erosive or plaque forms), their risk of malignancy was minimal.

Iocca et al. [15] performed a systematic review and meta-analysis to assess MT rates of Oral Potentially Malignant Disorders (OPMDs) and cancer risks of different subgroups of OPMDs. Their study was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology (MOOSE). They searched PubMed, Embase, and Scopus, up to 1 February 2019. Ninety-two OPMD studies satisfied the criteria for the analysis. Among the OPMD cases, forty-six reports were on OLP, and five were on OLL, and the numbers of patients analyzed were 14 362 LP and 449 OLL cases. The authors separately reported MT rates of different OPMD subgroups; for LP it was 1.4% (99% CI 0.9–1.9%), and for OLL, it was 3.8% (99% CI 1.6–7.00%).

Idrees et al. [16] performed a systematic review and meta-analysis, using strict clinicpathological inclusion criteria, to more precisely estimate the MT rate of OLP and the attribution of associated risk factors. Their strict criteria included: (a) the documentation of a clinician-verified OLP diagnosis, (b) cancer development properly documented at the same site as the OLP lesion, and (c) a minimum follow-up of six months prior to cancer development. Thirty-three primary studies were included in their analysis, covering a total of 12 838 reported OLP patients. The initial reports had documented 151 cases that had, over the follow-up period, progressed to carcinoma (1.2%). When the authors had applied their strict criteria as mentioned above, only 56 cases were deemed to have developed cancer (0.44%), Clinical subtypes were known for 47 cases. Thirty-four were associated with red OLP (more than two-thirds) in comparison with white OLP ($n = 13$) (white: OR = 0.37; CI 0.15–0.90). The tongue was the most frequent location of carcinomas ($n = 26$), followed by the buccal mucosa ($n = 15$). Those with a higher risk were smokers with OLP (OR = 4.62;

CI: 1.88–11.35), or those who consumed alcohol (OR = 3.22; CI 1.02–10.13), and those found to be seropositive for HCV (OR = 3.77; CI 1.14–12.52).

González-Moles et al. [17] undertook a systematic review of the published scientific literature on MT of OLP and, using the quality of evidence, ranked them to select the best 10 publications on the topic. Their protocol (available from the authors) closely followed PRISMA-*p* reporting guidelines. PubMed, Embase, Web of Science, and Scopus databases were searched for studies published prior to November-2020. An amount of 89 studies that met their eligibility criteria were qualitatively evaluated using the QUIPS tool. The final sample of 10 high-quality studies included 3403 patients, 3206 had OLP and 197 had a diagnosis of OLL. Among these, eighty out of OLP and six out of OLL patients developed OSCC. The meta-analysis demonstrated a pooled proportion of MT of OLP of 2.28% (95% CI = 1.49–3.20). OLL showed a slightly lower MT of 2.11% (95% CI = 0.01–6.33). The differences in MT found between the OLP and OLL groups were not significant ($p = 0.880$).

In the latest published systematic review and meta-analysis, Li, J-W et al. [18] examined the evidence on the MT of what they termed Oral Lichenoid Conditions (OLCs). Under this umbrella term of OLCs, the authors included OLP, OLL, and what they termed Lichenoid Mucositis Dysplasia (LMD). The criteria published in 2003 were used to distinguish publications that either used these specific criteria or the WHO criteria published prior to 2003. An amount of 54 studies qualified for their analysis, and this included 24,277 patients. The pooled proportion for MT of OLCs was 1.07% (95% CI [0.82, 1.32]). The malignant transformation rates for the three groups, OLP, OLL, and LMD, were 0.94%, 1.95% and 6.31%, respectively. Lichenoid Mucositis Dysplasia (LMD) had the highest reported MT rates. The authors who had applied 2003 criteria reported a lower MT than those using the WHO criteria (0.86%; 95% CI [0.51, 1.22] vs. 1.01%;95% CI [0.67, 1.35]). Those with red OLP lesions (OR = 3.52; 95% CI [2.20, 5.64]), regular smokers (OR = 1.79; 95% CI [1.02, 3.03]), those reporting alcohol consumption (OR = 3.27, 95% CI [1.11, 9.64]), or those reporting HCV infection (OR = 2.55, 95% CI [1.58, 4.13]) were indicated to have an increased risk of MT. The authors highlighted that MT rates could differ if criteria published in 2003 are applied to diagnose OLP.

4. Discussion

There has been a discussion in academic journals whether OLP is a potentially malignant condition. Holmstrup [19], in a commentary, argued that the controversy of the premalignant potential of OLP was over, and this controversy was further discussed by Gonzalez Moles et al. [20]. Over the past two decades, good quality longitudinal, follow-up studies have been conducted by several authors, mostly from North America and Europe, providing evidence that a proportion of OLP cases may transform to cancer over a period of time. These studies have allowed the data to be analysed in systematic reviews and by meta-analyses. In this umbrella study, we have synthesized the evidence from eight systematic reviews to enable the reader to comprehend the evidence. A summary of MT rates (%) and risk ratios estimated in these systematic reviews is given in Table 1. It is important to recognize that there are some limitations found in several of these systematic reviews (Table 2), and future work needs to address these factors.

The immunological events that take place in the OLP were recently described by Vicic et al. [21]. The disease begins with the recognition of extrinsic antigens (yet unknown), and the response evoked by CD8+ T lymphocytes, with their subsequent activation, generates cytotoxicity directed towards the basal keratinocytes. Persistent chronic inflammation is considered to be the underlying mechanism that initiates and promotes the pathway to carcinogenesis. Chronic inflammation may aid the proliferation and survival of keratinocytes, harboring genomic alterations, and it is now widely accepted to promote dysplasia and cancer development [22,23]. The factors that could increase the risk of malignancy are discussed in the latest systematic review by Gonzalez Moles [19]. These include the following: (1) presence of dysplasia in OLP (OR: 6.22); (2) red lesions had 2.77 times more risk vs. white lesions; (3) tongue OLP showed 1.82 times more risk vs. other oral sites; (4) in

tobacco and alcohol users (RR 1.98 & 2.28); (5) in the presence of HCV infection (RR 4.46); and (6) in cases with longer follow-up periods. Exclusively reticular OLP had a minimal risk of malignancy. In studies that specify clinical and histopathology criteria, risk estimates are higher compared to studies that lack diagnostic criteria (OR: 1.61). The influence of immunosuppressive treatment for OLP on MT is not well researched.

Table 1. Summary of the results from eight published systematic reviews on OLP.

Study	No of Included Studies	Proportion with SCC	Pooled Proportion (95% CI)
Fitzpatrick et al., 2014; [6]	16	90/7806 (1.15%)	meta-analysis not performed
Aghbari et al., 2017; [7]	57	280/19,676 (1.42%)	1.1% (95% CI: 0.9–1.4%)
Giuliani et al., 2018; [8]	21	92/6559 (1.37%)	1.37% (95% CI: not reported)
González-Moles et al., 2019; [9]	82	375/25,848 (1.45%)	1.14% (95% CI: 0.84–1.49)
Iocca et al., 2019; [10]	46	190/14,362 (1.32%)	1.4% (95% CI: 0.9–1.9%),
Idrees et al., 2020; [11]	33	151/12,838 = 1.2% 56/12,838 = 0.44% *	1.20% (95% CI: not reported) 0.44% (95% CI: not reported)
González-Moles et al., 2021; [12]	10	80/3206 = 2.50% **	2.28% (95% CI: 1.49–3.20)
Li et al. 2023 [13]	54	331/24,277 = 1.36%	1.07% (95% CI [0.82, 1.32])

* Based on stricter criteria; ** Based on the 10 highest-quality studies.

Table 2. Limitations noted in the published systematic reviews.

Limitation	Systematic Review (First Author)
No protocol or a priori design of methods.	Fitzpatrick et al. [11]; Aghbari et al. [12]; Iocca et al. [15]; Li et al. [18];
English language restriction	Fitzpatrick et al. [11]; Aghbari et al. [12]; Giuliani et al. ([13]; González-Moles et al. [14]; Idrees et al. [16]; González-Moles et al. [17]; Li et al. [18];
Titles and abstracts were screened by a single reviewer.	Fitzpatrick et al. [11];
Meta-analysis not performed. Reasons not justified or discussed	Fitzpatrick et al. [11];
Mt ratios estimated by an unweighted average	Fitzpatrick et al. [11]; Idrees et al. [16];
Confidence intervals not estimated and/or reported.	Fitzpatrick et al. [11]; Giuliani et al. [13]; Idrees et al. [16];
Heterogeneity and their sources were not assessed, explained or discussed.	Fitzpatrick et al. [11]; Aghbari et al. [12]; Giuliani et al. [13]; Idrees et al. [16]; Li et al. ([18];
Publication bias analysis not performed	Fitzpatrick et al. [11]; Giuliani et al. [13]; Iocca et al. [15]; Idrees et al. [16];

WHO histological typing of cancer and pre-cancer of the oral mucosa does not include the term lichenoid dysplasia. Instead, it states that dysplastic changes are sometimes seen in lichen planus. [24]. Van der Meij et al. [25], while modifying the WHO criteria (a proposal that was incidentally not ratified in any WHO documents), proposed the exclusion of epithelial dysplasia while diagnosing OLP. They favored the diagnosis of OLL in biopsies of OLP that demonstrated epithelial dysplasia. Their contradictory views and the subsequent revision of diagnostic criteria of OLP [26] have led to an underdiagnosis of OLP and underestimation of its malignant risk. Using strict diagnostic and inclusion criteria, Idrees et al. [16] estimated a very low malignant transformation rate for OLP (0.44%). Sivapathasundharam et al. [27], in their commentary, raise an important point—that a case of OLP, which may not show dysplastic features during initial examination but shows signs of dysplasia during subsequent follow-ups, cannot be suddenly re-diagnosed as

OLL owing to the appearance of dysplasia. Because OLP is a potentially premalignant disorder, dysplasia may represent a natural step in the development of SCC. Therefore, OLL, proposed by van der Meij et al. [25], should be considered as a continuum of OLP [28]. In a comparative study of OLP without dysplasia and OLP with dysplasia (which the authors termed as oral lichenoid dysplasia), the OLP group with dysplasia (3/44; 6.81) had a significantly higher MT than OLP without dysplasia (1/206; 0.49%) [29]. In a meta-analysis, Gonzalez-Moles [14] confirmed an increased risk of malignancy in OLP lesions, demonstrating epithelial dysplasia.

Based on the evidence presented in several systematic reviews appraised here, there is clear evidence that OLP carries a risk of malignant transformation. It is important to note that the relative risk is small compared to other OPMDs [30].

While the potentially malignant nature of OLP has been confirmed in the observational studies and systematic reviews, as discussed here, assessing the risk of malignancy in an individual OLP patient remains a challenge. Sagari et al., in a review, found no prognostic molecular biomarkers to identify which OLP lesions are at a higher risk for progression [31]. Epithelial cell proliferation is increased in OLP cases that transform to cancer [32]. In a retrospective study involving 56 OLP patients, aneuploid dysplastic lesions were shown to develop SCC more frequently than diploid lesions [33]. These results need further verification in larger, well controlled prospective studies.

4.1. Limitations

The exclusion of non-English articles in the present study should be discussed as a potential limitation. It is important to note, however, that some of the information included in this review was previously investigated from ancestry searches not restricted by publication language [6]. This approach gives us permission to rule out the potential risk of language bias, a form of selection bias frequently encountered in systematic reviews. We also noted some limitations in several of the systematic reviews that were analysed in this study. These limitations are listed in Table 2.

4.2. Future Prospectives

Primary research on OLP patients with long-term follow-up, evaluating MT, has mostly been reported in studies from North America and Europe. It would be of interest to see if MT rates are similar or not in other populations. The authors of the research publications and the systematic reviews have used several different definitions for OLP and OLL. A set of guidelines for conducting studies on OLP estimating MT was given by Gonzalez Moles et al. [10]. We would recommend that internationally agreed guidelines be developed by an expert working group (such as the World Workshop on Oral Medicine (WWOM)) to recommend whether OLL should be considered as a subgroup of OLP, rather than a separate disease entity. A wider discussion and an agreement are needed on how to report on a biopsy specimen if epithelial dysplasia is found in a clinically representative OLP case. An audit of local or systemic immunosuppressive treatment that OLP cases may have received in the past should be undertaken in future studies to investigate whether such interventions could play a role in MT.

4.3. Conclusions

Based on the current evidence, the clinical type and the histologic dysplasia assessment by an experienced oral pathologist may guide the clinician in risk assessment. Due to the potentially malignant nature, albeit of lower risk, OLP patients should be monitored regularly by their dentists to detect any early cancer development.

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Appendix A. Summary Search Strategy

Database	Query	Results	Upper Date Limit
MEDLINE (PubMed)	("Lichen Planus, Oral"[Mesh] or "oral lichen planus"[All Fields] or "olp"[All Fields] or "oral lichenoid lesion"[All Fields] or "oll"[All Fields]) and (malign* or premalign* or "potentially malignant disorder" or "precancer" or "cancer"[All Fields] or "Carcinoma, Squamous Cell"[Mesh] or "squamous cell carcinoma"[All Fields] or "oscc"[All Fields] or "transformation" [All Fields] or "risk"[All Fields] or "progression"[All Fields])	1628	May 2023
Embase	('oral lichen planus'/exp OR 'oral lichen planus' OR 'olp' OR 'oral lichenoid lesion' OR 'oll') AND ('malign*' OR 'premalign*' OR 'potentially malignant disorder' OR 'precancer'/exp OR 'precancer' OR 'cancer'/exp OR 'cancer' OR 'squamous cell carcinoma'/exp OR 'squamous cell carcinoma' OR 'oscc' OR 'transformation'/exp OR 'transformation' OR 'risk'/exp OR 'risk' OR 'progression')	2284	May 2023
Web of Science	TS = ("oral lichen planus" OR "olp" OR "oral lichenoid lesion" OR "oll") AND TS = ("malign*" OR "premalign*" OR "potentially malignant disorder" OR "precancer" OR "cancer" OR "squamous cell carcinoma" OR "oscc" OR "transformation" OR "risk" OR "progression")	2084	May 2023
Scopus	TITLE-ABS-KEY(("oral lichen planus" OR "olp" OR "oral lichenoid lesion" OR "oll") AND ("malign*" OR "premalign*" OR "potentially malignant disorder" OR "precancer" OR "cancer" OR "squamous cell carcinoma" OR "oscc" OR "transformation" OR "risk" OR "progression"))	1749	May 2023
Total		7745	

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