Malignant transformation rate of oral leukoplakia—systematic review

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Objective. The aim of this study was to perform a systematic review of prevalence studies to determine the rate of malignant transformation of oral leukoplakia and assess the influence of demographic factors (age, gender, and geographic region) on the overall transformation rate.

Study Design. A search was conducted for publications until July 2019 in 4 electronic databases and peer-reviewed journals. A manual search was performed on the bibliographies of the collected articles, and the authors were contacted for additional information. This study was previously registered with the trial number CRD42019126909 and study quality assessed through established methods. The results were expressed by means of proportions or odds ratios with a 95% confidence interval. Meta-regression was undertaken to evaluate possible sources of heterogeneity, and funnel plot visual analysis was performed to assess publication bias.

Results. The 34 observational epidemiologic studies included reported data on 26,209 patients with oral leukoplakia from 18 different countries. Meta-analysis of 32 studies (23,489 patients) presented an estimated overall mean proportion of malignant transformation rate of 9.70% (7.80−11.70) (I^2 = 98.66%; $\tau^2 < 0.001$; χ^2 = 23.18; degrees of freedom [df] = 31). When comparing genders, the odds ratio favored males with 0.622 (0.468−0.826) (I^2 = 29.77%; τ^2 = 0.089; χ^2 = 22.78; df = 16).

Conclusions. Within the limitations of the included studies in this systematic review, the results suggest that the malignant transformation rate was dependent on demographic factors and follow-up time. Future studies should include the development of guidelines to standardize the methodology for long-term follow-up assessment, thus reducing the risk of bias. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:600−611)

Both oral and pharyngeal cancers are the sixth most common cancers in the world and represent a significant public health problem not only because of the morbidity they cause but because they continue to be fatal when detected in the late stages.[1] According to GLOBOCAN 2012, lip and oral cancers caused 145,000 (1.8%) deaths worldwide, with new cases worldwide being estimated at 300,373 (2.1%).[2] Many authors currently consider that the most oral cancers arise from oral potentially malignant disorders (OPMDs) or oral potentially malignant lesions (OPMLs), of which oral leukoplakia (OL) is the most prevalent and well known.[3-6] This suggests that there is a need to diagnose not only oral cancer in the early stages but also OPMDs/OPMLs. A recent systematic review reported that OL has the highest prevalence among OPMLs worldwide, at 4.11%.[5]

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For clinicians, the greatest challenge continues to be the ability to predict which OL lesions will progress to oral squamous cell carcinoma.[4] Hence, the prevalence of OL is of greater importance than its malignant transformation rate (MTR); determining the prevalence will allow the practitioner to choose the most effective therapeutic approach, with an emphasis on patient-centered outcomes in clinical decision making. Because most leukoplakias are asymptomatic, the first goal of treatment should be the prevention of oral squamous cell carcinoma. A variety of treatment modalities have been proposed, but some studies,[7,8] including the latest Cochrane review,[9] have concluded that none seems to be effective in preventing cancer development in patients with OL. Although surgical removal remains the treatment of preference for most clinicians, there are no randomized controlled trials comparing surgical treatments with other treatment options, so at present, there are no accepted guidelines for OL treatment.[9]

Some characteristics, such as gender, OL location, lesion size, time from first diagnosis, morphologic

Statement of Clinical Relevance

Most oral cancers develop from pre-existing lesions, oral leukoplakia being the most prevalent and well known. The early detection and treatment of leukoplakia have been debated, and one of the greatest challenges is identifying lesions that will undergo malignant transformation.

characteristics, tobacco consumption, and grades of dysplasia have been described as risk factors for cancer development.[10] Nevertheless, currently, there are still no definitive, evidence-based, and clinically useful predictors of malignant transformation of OL.[9]

The estimate rates of malignant transformation of OL are uncertain and vary greatly among studies.[11-14] Differences among publication dates, study populations, study designs, and follow-up periods cannot be underestimated,[10,15] making comparison difficult.

Because of the relatively high prevalence of OL and its potential for malignancy, it is important to assess the MTR. In the past 5 years, an increase in available information has been observed, with the publication of several studies on this subject from different geographic regions.

The aim of this systematic review is to answer the following questions:

- In a population with an initial diagnosis of OL, what is the malignant transformation rate?
- Do demographic factors (age, gender, and geographic region) influence the overall malignant transformation rate?

This review has been categorized as Level 4a (systematic review of descriptive studies).

MATERIAL AND METHODS

Protocol and registration

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[16] and previously registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO; trial No. CRD42019126909).

Eligibility criteria

Observational epidemiologic studies in humans assessing the malignant transformation of OL were included. For the purposes of the review, only patients with a clinical and/or histologic diagnosis of OL and with no other concomitant conditions were eligible. From articles that included other pathologies, such as oral lichen planus or keratosis, only patients with OL diagnosis and no other concomitant lesions were considered.

"Time to malignant transformation" was defined as the time between initial diagnosis and progression to confirmed oral cancer. Two criteria were considered when confirming malignant transformation: (1) A malignant lesion had to occur at the same anatomic site as the original leukoplakia lesion.[17-19] Although some authors reported cancer development at sites different from that of the original OL lesion,[11,20,21] based on oral field malignancy,[22] cancer is considered a multifactorial disease in which different risk factors, such as tobacco, can play a role. Thus, in contrast to conditions associated with an increased risk for oral cancer (OPMDs), where the malignancy can arise in any location of the oral cavity, OPML malignancy can only be considered to be valid if cancer arises in the same oral subsite of the previous lesion. (2) A minimum of 6 months was required between initial diagnosis and histologic confirmation of malignancy. According to the World Health Organization criteria, a period less than 6 months between initial diagnosis and malignancy may suggest simultaneous occurrence of OL and cancer, leading to an overestimated MTR of OL.[19]

The following exclusion criteria were applied: (1) studies with samples partially analyzed in other studies that were also included or were based on the same cohort of leukoplakia cases but were reported at different follow-up times; (2) studies in which the MTR of OL was not clearly reported or could not be calculated; (3) studies in which the oral cancer diagnosis was determined in less than 6 months after OL diagnosis.

Data source and search strategy

An electronic database search was carried out on 4 electronic databases (PubMed, LILACS, Cochrane Collaboration, Embase) by using a combination of the MeSH terms "Leukoplakia"[Mesh] OR "Outcome Assessment (health care) [Mesh]" and the keywords "oral leukoplakia" OR "malignant transformation" OR "follow-up" for studies published until March 1, 2019.

An additional search of the gray literature was undertaken at the Proquest database, and the bibliographic references of the selected studies were manually assessed for additional evidence on the subject of this review.

This search was repeated on a later date (July 17, 2019), and 2 new articles fulfilling the inclusion criteria were identified and added.[18,23]

When possible, for the potentially relevant articles or for those with data that needed further clarification, the corresponding authors were contacted via email and asked about additional research work on the subject, or if they were aware of any ongoing projects that could be accessed.

Study selection and data collection

Study selection was based on a 3-stage assessment. In the first stage, all titles and abstracts were screened according to the eligibility criteria by 2 independent reviewers. In the second stage, the full texts of the relevant articles were analyzed, and the same eligibility criteria were applied. In the third stage, the selected articles were subjected to critical appraisal in terms of their scientific merit.

Data collected from the articles included in final selection consisted of (1) study characteristics: author, year of publication, country, study design (prospective or retrospective); (2) demographic data: sample size, mean age (years), and gender (male/female); and (3) outcome measures: OL MTR (absolute numbers), time to malignant transformation (months), and location of lesions.

Quality assessment

The Joanna Briggs Institute Critical Appraisal tools for use in the Joanna Briggs Institute (JBI) Systematic Reviews − Checklist for Prevalence Studies[24] was applied to assess the methodologic quality of the included studies and to determine the extent to which a study had addressed the possibility of bias in its design, conduct, and analysis. Two reviewers (D.M. and A.C. P.) independently assessed the included studies and scored each question (Yes, no, unclear, or not applicable). Any discrepancies were discussed until consensus was reached. Cohen's kappa (κ) coefficient ± asymptotic standard error was used to evaluate the interrater agreement for individual questions and the overall score,[25] with kappa values less than 0 considered as having the lowest agreement; 0.01 to 0.20 slight agreement; 0.21 to 0.fair agreement; 0.41 to 0.60 moderate agreement; 0.61 to 0.80 substantial agreement; and 0.81 to 0.99 almost perfect agreement.[25] The final score of each study was calculated on the basis of the percentage of positive answers ("yes") only. The risk of bias (RoB) of each study was subsequently categorized according to the final score as "high" ($\leq$ 49%), "moderate" (50%−69%), or "low" ($\geq$ 70%).[26] After the overall appraisal, none of the studies was excluded; however, 29.4% of the studies presented a score of 49% or less.

Statistical analysis

All data regarding the variables in the study were collected by using an Excel document. The pooled OL MTR was calculated on the basis of the data reported in the included studies. Data were processed by using a random-effects model (Dersimonian-Laird test) using OpenMeta[Analyst] v. 10.12 (http://www.cebm.brown.edu/openmeta/) software. Results were presented as forest plots displaying the untransformed proportions of MTR and prevalence odds ratios (OR) with the corresponding 95% confidence interval (CI). Heterogeneity among the studies was assessed with τ^2 (estimate of between-study variance). The Q-Cochran test according to Dersimonian and Laird (occurrence of heterogeneity) and the I^2 statistic were used to measure the proportion of statistical heterogeneity of the defined outcomes, quantified as low (25%), moderate (50%), or high (75%). Significant heterogeneity was considered to be present if I^2 was 50% or greater.[27] Meta-regression was conducted to identify possible sources of between-study heterogeneity in the pooled proportion estimates by using gender or geographic region as a categorical explanatory variable and average time of follow-up as the continuous variable.[27] Omnibus tests were performed to assess explainable variance for each evaluated source. Funnel plot visual analysis was undertaken to assess publication bias by using RevMan software (RevMan v5.3.5; Cochrane Collaboration, Denmark). Statistical significance was set at $P < .05$.

RESULTS

Literature research and included studies

The PRISMA search flow diagram is shown in Figure 1. After phase 1, 74 articles were included for full-text review. In phase 2, 44 studies were excluded for not complying with the inclusion criteria (Supplemental Table S1; available online). In addition, 4 records were identified through manual search of the reference list from the relevant studies, resulting in 34 studies accepted for qualitative evaluation and 32 for quantitative evaluation.

Interrater agreement and quality assessment

The results of Cohen's kappa interrater reliability for the 34 studies subjected to the JBI critical assessment ranged from 0.60 to 0.88, with an average kappa of 0.76 ± 0.04, which is considered to be substantial agreement, with mean JBI score of 63.39% (55.34%−71.45%) (moderate RoB). Ten studies were classified as having high RoB,[12,20,21,28-34] 6 had moderate RoB,[7,23,35-38] and 18 had low RoB.[11,13,14,17-19,39-50] The meta-regression conducted to assess the JBI score as a possible confounding factor revealed an omnibus P value of .46, which excluded JBI score as a factor in the heterogeneity when assessing MTR. On the basis of the individual analysis of the JBI checklist, the lowest individual scores were obtained for sample size selection, standardization and reliability of diagnosis, and statistical analysis (Q3, Q7, and Q8).

In this study, the JBI questions "Was the data analysis conducted with sufficient coverage of the identified sample?" and "Was the response rate adequate, and if not, was the low response rate managed appropriately?" (Q5 and Q9) were considered "'not applicable" when most of the studies used data concerning convenience samples from the clinical files of diagnostic centers, and therefore, the number of dropouts was considered irrelevant.

Study characteristics and synthesis of results

Table I summarizes the information collected from the selected studies. These studies included data from at least 26,209 patients diagnosed with OL from 18 different countries: Australia,[23] China,[18,19] Croatia,[39] Denmark,[7,13,20] Hungary,[14] India,[11,28,47] Iran,[44] Ireland,[48],

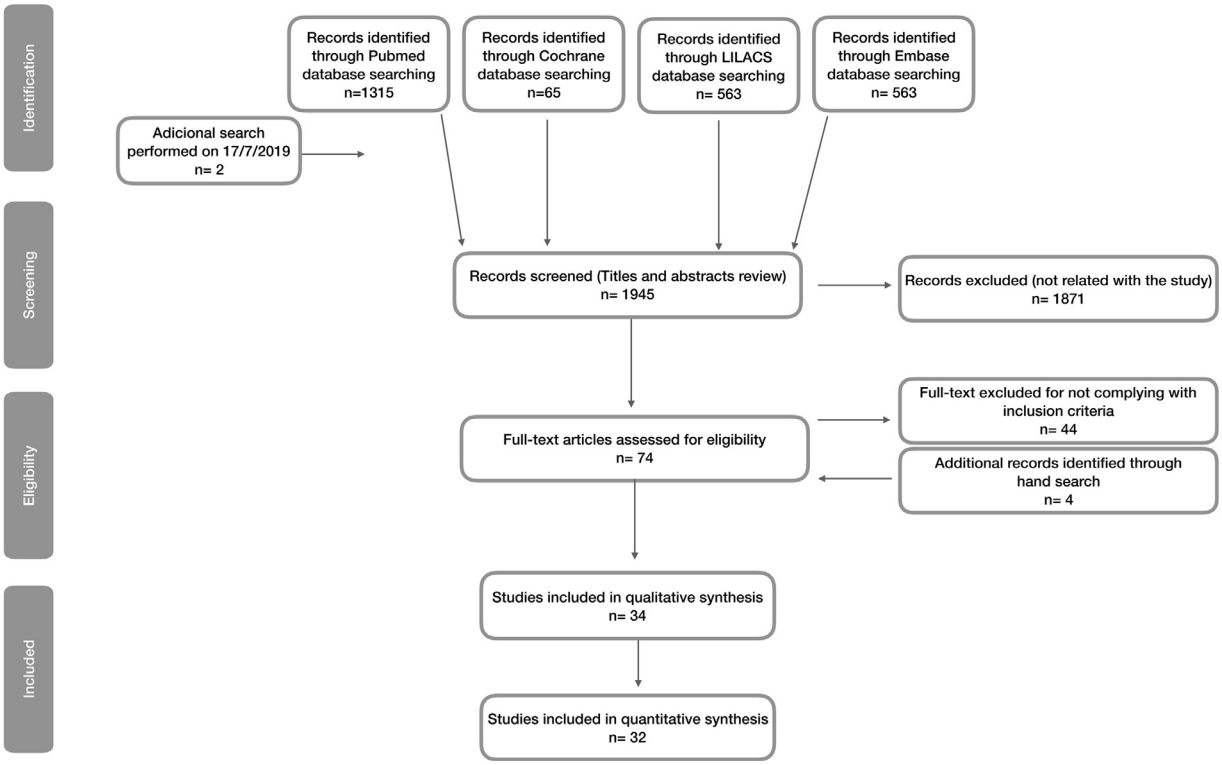

Fig. 1. Flow chart summarizing the search strategy and results.

Italy,[34,50] Japan,[32] The Netherlands,[31,37] Norway,[30] Spain,[42] Sweden,[35] Taiwan,[17,33,41,43,46,49] the United Kingdom, [21,29,38,40] the United States,[12,45] and Wales,[36] published between 1967 and July 2019.

All the articles in Table I were submitted to a narrative synthesis (systematic review; n = 34) and 32 were submitted to a quantitative analysis (meta-analysis).

The 2 studies not included in meta-analysis (corresponding to 2720 patients) reported cumulative risk and Kaplan-Meier transformation rates instead of the absolute numbers of cases with malignant transformation.[33,46] Thus, the total number of OL cases with malignant transformation considered for quantitative analysis was 23,489.

In 3 of the included studies, the OL diagnosis was exclusively clinical,[11,33,41] whereas in 26 studies, it was made on the basis of clinical examination results and confirmed with histologic examination[7,10,12-14,17-19,21,23,28-34,36,38-40,42-44,49,50] In 3 studies, the diagnosis criteria were not specified[20,45,46]; in 2 studies, some cases were diagnosed only clinically and others histologically[35,37]; and in another study, the diagnosis was based on histologic analysis in cases with suspicious lesions.[47]

1. *Malignant transformation rate and country:* We analyzed 23,489 OL cases from 18 different countries; of these cases, 1762 lesions underwent malignant transformation. The estimated overall mean proportion of MTR was 9.70% (7.80%−11.70%). The forest plot, subgrouped per country by using the random-effects model (Figure 2), presented high heterogeneity (I^2 = 98.66%; $\tau^2 < 0.001$; χ^2 = 23.18; df = 31), except for The Netherlands and Italy. However, this occurred without any statistically significant differences ($P > .05$) among countries. A meta-regression was performed to assess country as a heterogeneity factor for the MTR of OL, resulting in a statistically significant omnibus P value ($P < 0.001$), thus confirming country as a possible heterogeneity factor.
2. *Malignant transformation rate and gender:* Seventeen studies describing malignant transformation of OL according to gender were included in the meta-analysis. When comparing the MTR of OL in males (7.20% [5.00%−9.50%], with I^2 = 94.03%) and females (12.60% [7.50%−17.80%], with I^2 = 94.18%), no statistically significant differences were found ($P > .05$). However, the odds ratio favored males with lower odds of 0.62 (0.47−0.83) (τ^2 = 0.089; χ^2 = 22.78; df = 16) and I^2 (29.77%, moderate heterogeneity) (Figure 3). No bias was revealed in the funnel plot for publication bias assessment.
3. *Malignant transformation rate and average time of follow-up:* Twenty-seven studies reported the mean duration of follow-up and were included in the meta-analysis. The meta-regression omnibus P

Table I. Data collected from included articles

Author	Year of publication	Country	Study design	Leukoplakia (n)	Age (years)	Gender	Mean duration of follow-up (years)	Cases at follow-up	Cases with malignant transformation	Gender of patients with malignant transformation	Time to malignant transformation (years)	Location of cancer lesions
Einhorn & Wersall	1967	Sweden	Retrospective	832	20−49 years: 274; 30−69 years: 399; 70−89 years: 109	M: 522; F: 260	11.7	782	12 (for the first 5 years)	Not specified	1.3% during the first 3 years; 1.6% after 5 years; 2.4% after 10 years; 4% after 20 years	
Pindborg et al.	1968	Denmark	Retrospective	248	Not specified	M: 133; F: 81	3.7	214	8	M: 5; F: 3	Not specified	4 buccal mucosa; 1 lateral border of the tongue; 1 alveolar ridge; 1 floor of mouth; 1 lower buccal groove
Roed-Petersen	1971	Denmark	Retrospective	331	Not specified	M: 192; F: 139	4.3	331	9 (Overall: 12)	M: 4; F: 8	Not specified	For carcinomas, the site of predilection was the margin of the tongue (4 of 9)
Gangadharan & Paymaster	1971	India	Retrospective	1411	M: 45; F: 49,5	M: 1147; F: 264	Not specified	626	49	M: 35; F: 14	50% of the leukoplakias which developed cancer at the same site did so within 2 years	35 buccal mucosa; 14 anterior two-thirds of the tongue
Silverman et al. (A)	1976	India	Prospective	6718	35−39 years: 9.6%; ≥ 65 years: 14.6%	M: 4687; F: 75	2	4762	6	M: 5; F: 1	Not specified	2 buccal mucosa, 2 commissure, 1 labial mucosa, 2 gingiva
Banoczy	1977	Hungary	Retrospective	890	21−30 years: 15; 31−40 years: 67; 41−50 years: 132; 51−60 years: 201; 61−70 years: 182; ≥ 71 years: 73	M: 510; F: 160	9.8	670	40	M: 26; F: 14	Not specified	37.5% tongue; 15% lips; 12.5% floor of the mouth; 12.5% buccal mucosa; 7.5% commissures; 7.5% alveolar ridge; 5% hard palate; 2.5% soft palate
Kramer et al.	1978	United Kingdom	Retrospective	46	20−29 years: 2; 30−39 years: 3; 40−49 years: 14; 50−59 years: 11; 60−69 years: 19; 70−79 years: 8; not known: 3	M: 27; F: 36	4.2	29	7	Not specified	Not specified	Sublingual
Pogrel	1979	Wales	Retrospective	19	48−73 years	M: 7; F: 12	≥ 5	19	3	M: 2; F: 1	4, 5, and 7	Sublingual
Gupta et al.	1980	India	Prospective	502	Not specified	Not specified	10	502	11	Not specified	Not specified	Not specified
Roch-Berry	1981	United Kingdom	Retrospective	117	Not specified	M: 68; F: 49	Not specified	117	20	M: 16; F: 4	Not specified	20 tongue
Silverman et al. (B)	1984	USA	Prospective	257	54 years (range 20−89 years)	M: 125; F: 132	7.2	257	45	M: 19; F: 26	8.1	13 tongue; 11 gingiva; 7 floor of the mouth; 5 buccal mucosa; 5 palate; 4 lip
Lind	1987	Norway	Retrospective	157	57.7 years	M: 102; F: 55	9.3	157	14	M: 8; F: 6	5.5	4 tongue; 4 buccal mucosa; 3 gingiva; 2 lower sulcus; 1 labial mucosa
Hogewind et al.	1989	Netherlands	Retrospective	84	16−30 years: 6; 31−45 years:17; 46−60 years: 24; > 60 years: 37	M: 50; F: 34	2.5	46	3	M: 0; F:3	4.2	3 lateral border of the tongue and floor of the mouth
Schepman et al.	1998	Netherlands	Retrospective	166	57 years (23−91 years)	M: 76; F: 90	2.42	166	20	M: 4; F: 16	2.67	15 tongue and floor of the mouth (total = 101); 5 other oral subsites (total = 65)
Saito et al.	1999	Japan	Prospective	111	52.5 years	M: 62; F: 49	4	111	8	Not specified	9 years for localized malignancy; 4 years for widespread malignancy	Not specified

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Table I. Continued

Author	Year of publication	Country	Study design	Leukoplakia (n)	Age (years)	Gender	Mean duration of follow-up (years)	Cases at follow-up	Cases with malignant transformation	Gender of patients with malignant transformation	Time to malignant transformation (years)	Location of cancer lesions
Napier et al.	2003	Ireland	Retrospective	50	58 years (13−88)	M: 18; F: 32	8.15 (1.8−14.5)	50	17	M: 4; F: 13	5.9	7 tongue; 3 buccal mucosa; 2 retromolar pad; 2 2; 1 hard 1; 1 anterior pillar of fauces; 1 floor of the mouth
Holmstrup et al.	2006	Denmark	Retrospective	169	60.6 years	M: 63; F: 84	5.5	169	7	Not specified	6.6	Not specified
Hsue et al.	2007	Taiwan	Retrospective	423	47.5 years	Not specified	3.44	423	15	Not specified	3.44	Not specified
Yen et al.	2008	Taiwan	Retrospective	491	39 years	M:491	20	491	Not specified	Not specified	Not specified	Not specified
Arduino et al.	2009	Italy	Retrospective	207	63.8 years	M: 107; F: 100	4.5 (1−16)	207	15	M: 9; F: 6	2.5	9 tongue; 3 buccal mucosa; 2 gingiva; 1 floor of the mouth
Warnakulasuriya et al.	2011	United Kingdom	Retrospective	335	Not specified	Not specified	9.04	335	23	Not specified	Not specified	Not specified
Brzak et al.	2012	Croatia	Retrospective	139	49 years	M: 60; F: 79	10	139	2	Not specified	4	Not specified
Ho et al.	2012	United Kingdom	Prospective	65	Not specified	Not specified	5	65	18	Not specified	4	Not specified
Liu et al.	2012	China	Retrospective	320	54.1 years (21−83)	M: 145; F: 175	5.1 (1−20 years)	320	57	M: 20; F: 37	4.5	38 of 121 lesions in lateral/ventral tongue
Wang et al.	2018	Taiwan	Retrospective	1898	45.8 ± 10.7	M: 1677; F: 221	4.6 ± 3.3	1898	102	Males had higher malignant transformation risk than females (hazard ratio [HR] 4.96%)	2	Not specified
Gandara-Vila et al.	2018	Spain	Prospective	85	58.68 ± 12.88	M: 45; F: 40	4.13 (5.58 for those who developed carcinoma)	85	6	M: 2; F: 4	Between 11 months and 11 years	6 of 39 lesions in tongue and floor of the mouth
Chuang et al.	2018	Taiwan	Prospective	5142	47	M: 5142	5	5142	161	M: 161	Not specified	Not specified
Qasrdashti et al.	2017	Iran	Retrospective	522	< 50 years: 173; > 50 years: 349	M: 210; F: 312	20	522	213	M: 69; F: 144	Not specified	115 tongue; 46 buccal mucosa; 30 floor of the mouth; 10 lower gingiva; 6 upper gingiva; 6 lips
Yanik et al.	2015	USA	Prospective	1526	Not specified	Not specified	Not specified	1526	647	Cumulative incidence of Oral cavity cancer after OL diagnosis was higher among females (5-year cumulative incidence = 2.73%)	Especially common ≤ 3 months after leukoplakia claim (cumulative incidence = 0.67%) After 3 months: Additional 0.43% of the population was diagnosed by 1 year; 1.45% was diagnosed between 1 and 5 years	For overall cohort: 2265 tongue; floor of the mouth 1018
Wang et al.	2014	Taiwan	Retrospective	2641	Not specified	M: 2250; F: 391	Not specified	2641	112	Not specified	2.3 years for epithelial dysplasia with hyperkeratosis/epithelial hyperplasia; 3 years for hyperkeratosis/ epithelial hyperplasia	57 buccal mucosa; 21 tongue; 15 gingiva; 10 lower lip; 5 soft palate; 4 floor of the mouth; 2 upper lip; 1 hard palate
Lian et al.	2013	Taiwan	Retrospective	2229	Not specified	M: 2229	14	2229	Not specified	Not specified	4	Not specified

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Table I. Continued

Author	Year of publication	Country	Study design	Leukoplakia (n)	Age (years)	Gender	Mean duration of follow-up (years)	Cases at follow-up	Cases with malignant transformation	Gender of patients with malignant transformation	Time to malignant transformation (years)	Location of cancer lesions
Mela et al.	1966	Italy	Retrospective	211	Not specified	M: 192; F: 67	3–11	141	5	Not specified	Not specified	Not specified
Wang et al.	2019	China	Retrospective	Overall cohort: 875; Cohort without proliferative verrucous leukoplakia: 835	< 50 years: 300; ≥ 50 years: 575	M: 374; F: 501	4.5	835	102	M: 35; F: 72	Not specified	57 of 340 lesions in the tongue; 25 of 314 in the buccal mucosa; 5 of 18 in the lip; 2 of 4 in the floor of the mouth; 11 of 111 in gums; 2 of 32 in the palate
Shearston et al.	2019	Australia	Retrospective	202	56.5 ± 12.1	M: 111; F: 91	1.5–14 (< 5 years:202 60; > 5 years: 142)		3	For overall cohort: M: 2; F: 3	5.2	40% tongue; 20% floor of the mouth; 20% alveolar ridge; 20% gingiva

value was .011 ($P < .05$) confirming the influence of the follow-up duration as a heterogeneity factor for the MTR of OL (Figure 4). Longer follow-ups are associated with higher odds of OL lesions being transformed into cancer.

4. *Malignant transformation rate and time to malignant transformation:* Twenty-one studies[7,11,12,17,19,23,30-32,35-37,39-42,45,46,48-50] reported the time to malignant transformation, although there were differences in the outcome presentation (absolute mean values in days months or years, time intervals, cumulative incidence). Thus, it was not possible to perform a meta-analysis.

Seventeen studies[7,11,12,19,30-32,36,37,39-42,46,48-50] described their results in terms of average time to OL malignant transformation, ranging from 11 to 132 months.

1. *Malignant transformation rate and age:* The ages of patients with OL was heterogeneously reported in 24 studies.[7,11,12,14,18,19,23,28-33,35-37,39,41-44,48-50] Only 11 of the 34 studies presented the age distribution of OL cases at the time of cancer diagnosis.[14,18,19,23,30,31,36,37,44,49,50] However, the age groups described in these studies were heterogeneous, and therefore, it was not possible to perform a meta-analysis. The majority of studies reported higher prevalence of OL malignant transformation in older individuals.
2. *Malignant transformation rate and clinical sites of lesions:* Twenty studies[11-14,17–21,23,28-31,36,37,42,44,48,50] indicated the number of cases by sites where malignant transformation occurred, but only 2 of them reported on the most affected site.[19,20] Two studies[29,36] only included sublingual OL lesions (n = 48), with 10 undergoing malignant transformation. Two studies reported the tongue and floor of the mouth together as the most affected sites.[31,37]

Most studies reported that the tongue was the most common site for the malignant transformation of OL.

DISCUSSION

In this systematic review with meta-analysis, the MTR of OL was studied as a primary outcome, and variables, such as geographic region, gender, follow-up period, time to malignant transformation, age, and clinical lesion location, were assessed to evaluate their importance in OL transformation.

The estimated overall mean MTR among the 32 studies included in the meta-analysis was 9.70%, which is higher than the 3.54% MTR reported in a previous systematic review.[51] However, 2 facts should be considered: (1) The sample size of this study is considerably larger

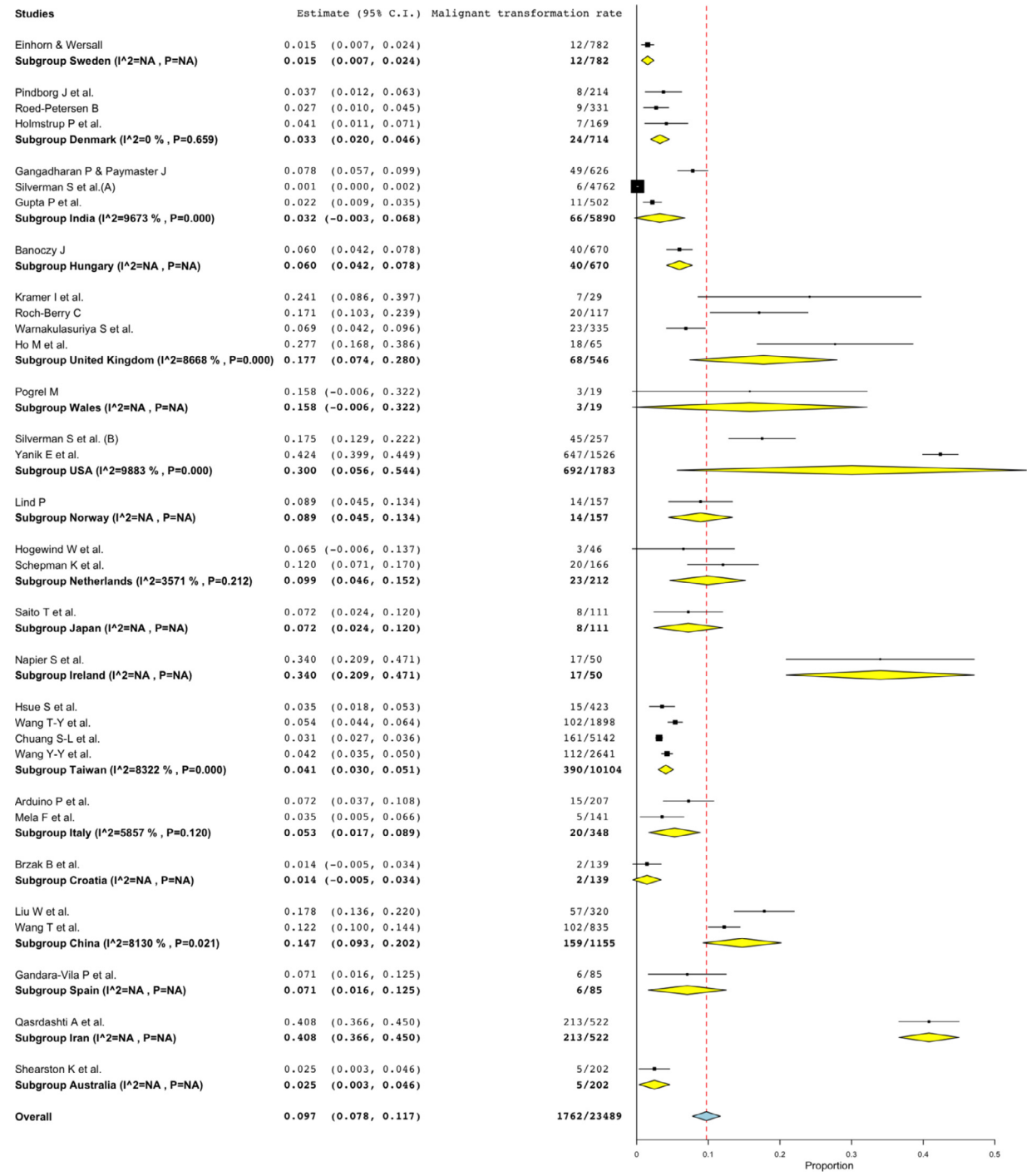

Fig. 2. Forest plot of oral leukoplakia malignant transformation rate subgrouped per country.

(n = 23,489) than the sample size of the 2016 systematic review (n = 11,423), and to the best of our knowledge, up to the set date, this is the largest sample studied regarding the subject; and (2) in our study, the estimated overall mean proportion of MTR was calculated by using the random-effects (Dersimonian-Laird test) model, which takes into account the effect of between-study variance, thus corresponding to a more robust statistical calculation than the simple arithmetical mean.[27]

When assessing study eligibility, discrepancies between the studies in terms of OL definitions and diagnosis criteria were observed, with the possibility of erroneous inclusion of a range of conditions under the umbrella clinical diagnosis of OL.[22] Through the years,

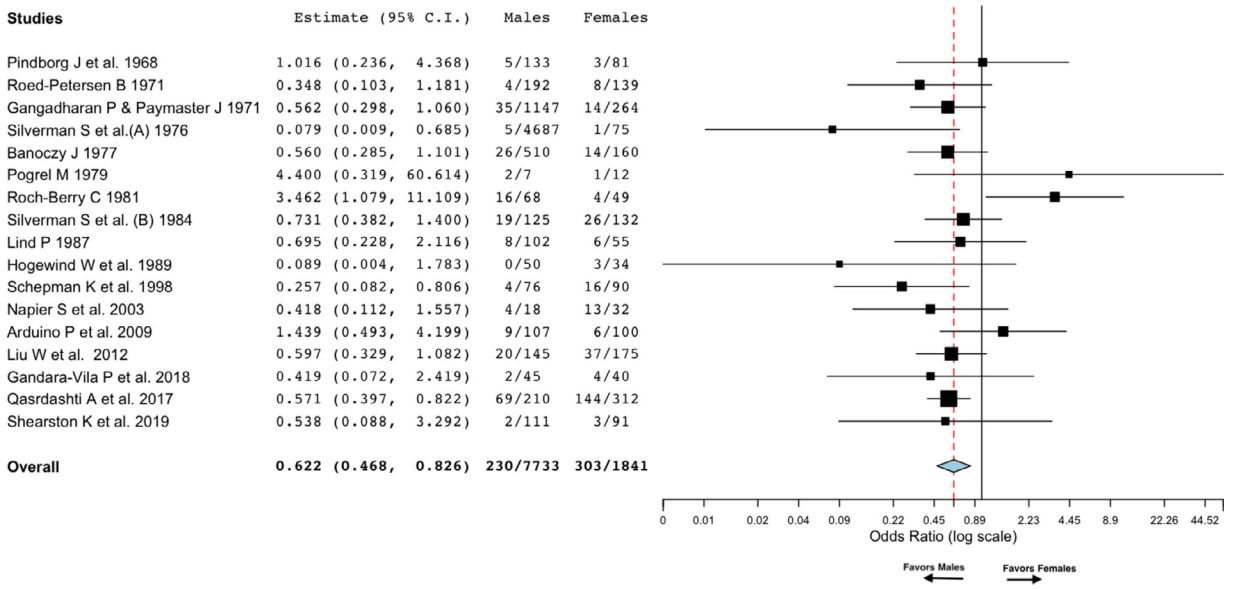

Fig. 3. Odds ratio forest plot for oral leukoplakia malignant transformation rate comparison between genders.

an improvement has been observed in OL definition and diagnosis criteria, and thus, some of heterogeneity could be attributed to the era of the publications.

The results also depend on the origin of the patients: Studies with random samples or screenings/house-to-house surveys generally report lower transformation rates compared with hospital-based studies or those with patients referred to specialized centers.[11,19,28,37,47]

Only cases where malignant transformation occurred at the same clinical site of a previous OL lesion[17–19] and the ones presenting only OL and no other concomitant lesions[44] were included in this meta-analysis. Some authors had described cancer development at sites different from that of the original OL lesion,[11,20,21] based on oral field malignancy.[22] Nevertheless, cancer is a multifactorial disease in which different risk factors, such as tobacco use, may play a role. Thus, in contrast to the conditions associated with an increased risk for oral cancer (OPMDs), where the malignancy can arise in any location of the oral cavity, an OPML malignancy can only be considered to be valid if cancer arises in the same oral subsite of the previous lesion.

With regard to the influence of demographic characteristics on the MTR of OL, it was possible to assess the impact of the geographic area, patient gender, and follow-up period.

The forest plot for MTR subgrouped by country population showed high heterogeneity, except in The Netherlands and Italy. There were, however, no statistically significant differences among the countries, and the meta-regression confirmed country as a possible heterogeneity factor. In fact, studies from distinct geographic areas reported different MTRs of OL, indicating that geographic area may play a role, essen-

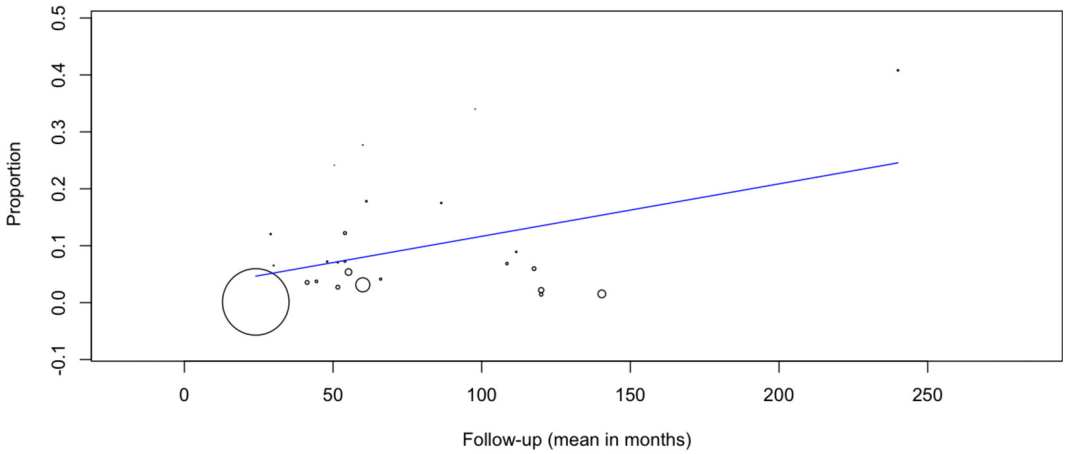

Fig. 4. Meta-regression regarding the influence of mean time of follow-up in the malignant transformation of oral leukoplakia (OL).

tially because of the different habits and genetics of the people living there. For example, the use of different forms of chewing tobacco (as betel or areca-nut) is a well-known risk factor, and consumption of these products is more common in Southern Asia.[47]

Although no statistically significant differences were detected between males and females with regard to the MTR, males presented lower odds of experiencing malignant transformation of OL. These results are in agreement with previously published studies, although it was not possible to find a clear reason for this.[14,23,30,37,48,51,52]

Time to malignant transformation was assessed in 21 studies, with variability in outcomes. Thus, it was not possible to perform a meta-analysis. The average time to malignant transformation reported in 17 studies ranged from 11 to 132 months. Furthermore, the meta-regression in follow-up time confirmed the influence of follow-up duration as a heterogeneity factor for the MTR of OL. Thus, longer follow-ups are associated with higher odds of OL lesions that transform into cancer. These results are in agreement with other studies.[12,37] There are no clear guidelines concerning the frequency of follow-up of patients with OL, but in general, it is accepted that examinations should be performed every 6 to 12 months as for any other examination for oral disease[53]

The qualitative analysis of studies presenting the age distribution of patients with OL at the time of cancer diagnosis showed a higher prevalence of malignant transformation in older patients, as reported in the literature.[18,37,51,54,55] This association between age and malignancy may suggest that patients who have persistent OL and are exposed to associated risk factors for longer periods are more prone to malignant transformation.[51,54]

Although some authors reported that there is no association between the intraoral location and a higher risk of malignant transformation,[7,13,37,52] others linked some OL locations to a higher risk, namely, the tongue,[12,18,20,30,44,54,56] and the floor of the mouth.[18,37] Lee et al. found that location has a strong impact on the risk of carcinoma in patients with OL lesions, reporting that the risk is 2.72-fold and 1.84-fold higher in those with OL of the tongue and OL of the floor of the mouth, respectively, compared with other subsites.[57] In their systematic review, Warnakulasuriya et al. reported that the malignant transformation of OL was most prevalent in the case of tongue lesions (24.22%), followed by the tongue and the floor of the mouth together (14.85%). In this systematic review, most studies reported that the tongue was the most common site for the malignant transformation of OL. The affected location may vary, depending on different populations in association with their habits. For example, some studies identified the buccal mucosa and the labial commissure as the locations with the highest MTR,[28,47] but this is particularly true of patients with tobacco chewing and smoking habits, which are more common in such countries as India.

The results of Cohen's kappa interrater reliability for the 34 studies presented an average JBI score of 0.76 ± 0.04, which is considered to be a substantial agreement between the 2 reviewers.[25]

One of the appraisal tools available for prevalence studies, the JBI checklist for use in prevalence studies, was used in this study. The objective of the JBI checklist for prevalence studies is to assess the methodologic quality of the study and to address the possibility of bias in the design, conduct, and analysis of the research. One of the most poorly addressed aspects of the analyzed studies was the use of an adequate sample size. Only 44.12% had a valid sample size for the described objectives. Another limitation of the included studies was the lack of standardization and reliability of the OL diagnosis. Clinical diagnosis can be performed by 1 or more clinicians if there is a calibration process between them, but in some of the included studies, some limitations were noted in the descriptions of clinical or research experiences and when there was more than 1 observer. The same limitations were found in histologic examination with regard to the calibration of pathologists. Also, in some of the included articles, the statistical analyses evaluated by the JBI assessment tool were poorly addressed, with the Methods section not having enough details to help identify the analytical technique used and the protocol to measure the addressed variables. According to the JBI levels of evidence, a systematic review of prevalence studies is categorized as Level 4a, corresponding to a low level of evidence with some degree of heterogeneity among the included studies. Thus, these results should be interpreted with caution with regard to external validity.

The limitations of this review are mainly related to the heterogeneity of the included studies, mostly the lack of uniformity in data reporting OL and its malignant transformation. Heterogeneity was found not only in data presentation (patient age, duration of follow-up, location of lesions) but also in the different diagnostic criteria used, mainly in older studies in which only clinical diagnosis was performed, which could interfere in the obtained results. In this systematic review, the potential risk factors (e.g., morphologic characteristics, tobacco consumption, and grades of dysplasia) for the malignant transformation of OL were not taken into consideration because of the lack of uniformity in the reported data. These factors could present an important role in the MTR of OL, although the available evidence does not allow for addressing their influence on the malignant transformation of OL lesions.

Follow-up studies are mandatory to assess the malignant transformation rate and are ideally performed with a prospective design that considers different

interventions and control groups. However, ethical issues may arise in studies on potential malignant diseases; this implies that most of the published studies have a retrospective design. Although not ideal, future studies with a retrospective design should make an effort to select an adequate sample size, with a standardized assessment of participants' demographic characteristics, risk factors, and diagnostic (clinical and histologic) criteria. Regular follow-ups are recommended to determine time to event by detecting small foci of carcinomas, thus allowing effective treatment of transformed lesions.

CONCLUSIONS

In summary, the results of this systematic review, with the largest sample size on this subject to date, suggest the existence of a higher malignant transformation rate than those reported by previous studies and that this rate is dependent on geographic region, gender (females with higher odds of OL undergoing malignant transformation), and follow-up period (longer follow-ups are associated with higher MTRs). Taking into account the outcomes and the limitations of this study, future research in the field of malignant transformation of OL should include the development of guidelines for conducting long-term follow-up studies to provide a more reliable methodology, thus reducing heterogeneity.

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Table S1. Articles excluded in phase two

Author	*Year of publication*	*Title*	*Reason*
Silverman S et. al	1968	Observations on the clinical characteristics and natural history of oral leukoplakia	Silverman S et al. (1984) has more recent data
Mehta F et al.	1969	Clinical and histologic study of oral leukoplakiain relation to habits	5-year follow-up of the same cohort of Gupta P et al. (1980)
Sugãr L & Banoczy J	1969	Follow-up studies in oral leukoplakia	Duplicated from Banoczy J (1977)
Mincer H et al.	1972	Observations on the clinical characteristics of oral lesions showing histologic epithelial dysplasia.	Epithelial dysplasia
Mehta F et al.	1972	Oral leukoplakia in relation to tobacco habits: a ten-year follow-up study of Bombay policeman	Same cohort of Gupta P et al. (1980)
Banoczy J & Sugãr L	1975	Progressive and regressive changes in Hungarian oral leukoplakias in the course of longitudinal studies	Same cohort of Banoczy J (1977)
Banoczy J & Csiba A	1976	Occurence of epithelial dysplasia in oral leukoplakia: Analysis and follow-up of 12 cases	Same cohort of Banoczy J (1977)
Mehta F et al.	1976	Incidence of oral leukoplakias among 20358 Indian villagers in a 7 year period	Same cohort of Gupta P et al. (1980)
Tyldesley W	1976	Tobacco chewing in english coalminers (2) Malignant transformation in a tobacco-induced leukoplakia	Without data about malignant transformation
Pindborg J et al.	1977	A follow-up study of sixty-one oral dysplastic precancerous lesions in Indian villagers	Same cohort of Pindborg J et al. (1968)
Mehta F et al.	1982	An intervention study of oral cancer and precancer in rural Indian populations: a preliminary report	Same cohort of Gupta P et al. (1980)
Gupta P et al.	1989	Na epidemiologic assessment of cancer risk in oral precancerous lesions in India with special reference to nodular leukoplakia	Same cohort of Gupta P et al. (1980)
Gupta P et al.	1990	A primary prevention study of oral cancer among Indian villagers. Eight-year follow-up results	Same cohort of Gupta P et al. (1980) and without data about malignant transformation
Kannan S et al.	1993	Ultrastructural variations and assessment of malignant transformation risk in oral leukoplakia	Transversal study, no follow-up reported
Lumerman H et al.	1995	Oral epithelial dysplasia and the development of invasive squamous carcinoma.	Description of white and red lesions, the number of leukoplakias that underwent malignant transformation couldn't be identified
Gupta P et al.	1995	Effect of cessation of tobacco use on the incidence of oral mucosal lesions in a 10-yr follow-up study od 12212 users	Same cohort of Gupta P et al. (1980)
Shiu M et al.	2000	Risk factors for leukoplakia and malignant transformation to oral carcinoma: a leukoplakia cohort in Taiwan	Case-control study
Cowan C et al.	2001	Potentially malignant oral lesions in Northen Ireland: a 20-year population based perspective of malignant transformation	The authors didn't identified oral leukoplakia
Pandey M et al.	2001	Evaluation of surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, India	The authors didn't report cases of leukoplakia with malignant transformation
Saito T et al.	2001	Development of squamous cell carcinoma from pre-existent oral leukoplakia: with respect to treatment modality	Experimental study
Shiu M & Chen T	2004	Impact of betel quid, tobacco and alcohol on three-stage disease natural history of oral leukoplakia and cancer: implication for prevention of oral cancer	Case-control study
Bornstein M et al.	2004	Oral leukoplakia. A retrospective study of clinical and histological data	Follow-up < 12 months
Nagao T et al.	2005	Incidence rates for oral leukoplakia and lichen planus in a Japanese population	No follow-up reported neither malignant transformation cases
Yang Y et al.	2005	Incidence rates of oral cancer and ora pre-cancerous lesions in a 6-year follow-up study of a Taiwanese aboriginal community	Transversal study, no follow-up reported

(*continued on next page*)

Table S1. Continued

Author	*Year of publication*	*Title*	*Reason*
Lee J et al.	2006	Carcinoma and dysplasia in oral leukoplakias in Taiwan: Prevalence and risk factors	Prevalence study, no follow-up reported
Roosar A et al.	2007	A long-term follow-up study on the natural course of oral leukoplakia in a Swedish population-based sample	No consistency between site of oral cancer and site of lesion
Silveira E et al.	2009	Lesões orais com potencial de malignização: anãlise clínica e morfológica de 205 casos	Transversal study, no follow-up reported; additional information requested via email but was not available
Yang S et al.	2009	Human papillomavirus in oral leukoplakia is no prognostic indicator of malignant transformation	Experimental study
Lan AX et al.	2009	Analysis of risk factors for carcinogenesis of oral leukoplakia.	Corresponding author didn't answer to the email requesting full-text
Liu W et al.	2010	Malignant transformation of oral leukoplakia: a retrospective cohort study of 218 Chinese patients	Cases duplicated with Liu W et al. (2012)
Vãzquez-Álvarez R et al.	2010	Correlation between clinical and pathologic diagnosis in oral leukoplakia in 54 patients	Transversal study, no follow-up reported
Pereira J et al.	2011	Epidemiology and correlation of the clinicopathological features in oral epithelial dysplasia: analysis of 173 cases	Transversal study, no follow-up reported
Wang YF et al.	2011	A retrospective analysis on the malignant transformation rate, time and risk factors of oral leukoplakia	Corresponding author didn't answer to the email requesting full-text
Liu W et al.	2011	Malignant transformation of oral epithelial dysplasia: clinicopathological risk factors and outcome analysis in a retrospective cohort of 138 cases	Cases duplicated with Liu W et al. (2012)
Gao Y et al.	2012	Clinicopathological characteristics of malignant transformation in 85 cases of oral leukoplakia.	Corresponding author didn't answer to the email requesting full-text
Brouns E et al.	2013	The relevance of uniform reporting in oral leukoplakia: definitio, certainty factor and staging based on experience with 275 patients	Not a follow-up study of leukoplakia, no information about malignant transformation
Starzyńska A et al.	2014	Oral premalignant lesions: epidemiological and clinical analysis in the northern Polish population	Interventional study
Brouns E et al.	2014	Malignant transformation of oral leukoplakia in a well defined cohort of 144 patients	Interventional study; email to corresponding author requesting information about the group with no intervention without answer
Goodson M et al.	2015	Oral precursor lesions and malignant transformation - who, where, what and when?	Not a follow-up study of leukoplakia
Kuribayashi Y et al.	2015	Long-term outcome of non-surgical treatment in patients with oral leukoplakia	Interventional study
Shetty P et al.	2016	Oral leukoplakia: Clinicopathological correlation and its relevance to regional tobacco-related habit index	Transversal study, no follow-up reported
Maia H et al.	2016	Potentially malignant ora lesions: clinicopathological correlations	Transversal study, no follow-up reported
Liu Y et al.	2017	Quantitative prediction of oral cancer risk in patients with oral leukoplakia	Not a follow-up study of leukoplakia, no information about malignant transformation
Goodson M et al.	2017	Efficacy of Oral Brush Biopsy in Potentially Malignant Disorder Management	Corresponding author didn't answer to the email requesting detailed information