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The malignant transformation of oral lichen planus and oral lichenoid lesions

A systematic review

Sarah G. Fitzpatrick, DDS; Stanley A. Hirsch, DDS, MS; Sara C. Gordon, DDS

A small subset of cases of oral lichen planus (OLP) have long been linked with the development of squamous cell carcinoma (SCC). The first critical evaluation of the literature regarding this link was presented by Krutchkoff and colleagues1 in 1978; they applied inclusion diagnostic criteria to cases reported as OLP with malignant transformation, and they found many cases to be lacking in evidence. van der Meij and colleagues2 used the same criteria for including cases in a review of the malignant transformation of OLP in 1999, and these investigators also found that the majority of cases presented in the literature could not be included owing to a lack of documentation regarding the clinical and histologic features of the cases. Nonsystematic reviews by Mattsson and colleagues3 in 2002 and Gonzalez-Moles and colleagues4 in 2008 showed that the transformation rates in the studies they evaluated ranged from 0.4 to 5.6 percent and from 0 to 12.5 percent, respectively. A somewhat more accepted estimated range has been considered to be 0.5 to 2.0 percent.3

One key difficulty in evaluating the malignant transformation of OLP is the comparability of

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ABSTRACT

Background. Determining the potential for malignant transformation of oral lichen planus (OLP) is complicated by difficulties in diagnosis, differentiation from oral lichenoid lesions (OLLs) and the phenomenon of premalignant lesions’ exhibiting lichenoid characteristics. The authors of this systematic review evaluated evidence regarding malignant transformation of OLP and characterized transformation prevalence, clinical characteristics of OLP lesions developing into squamous cell carcinoma (SCC) and time to transformation.

Types of Studies Reviewed. The authors searched PubMed, Embase and Thomson Reuters Web of Science in a systematic approach. They evaluated observational English-language studies involving human participants published in peer-reviewed journals. Inclusion required patients to have the diagnosis of OLP or OLL as confirmed with biopsy results on initial enrollment. They excluded all patients who had dysplasia on initial biopsy of OLP or OLL lesions.

Results. Sixteen studies were eligible. Among 7,806 patients with OLP, 85 developed SCC. Among 125 patients with OLL, four developed SCC. The rate of transformation in individual studies ranged from 0 to 3.5 percent. The overall rate of transformation was 1.09 percent for OLP; in the solitary study in which investigators evaluated OLL, the rate of transformation was 3.2 percent. Patients’ average age at onset of SCC was 60.8 years. The authors noted a slight predominance of female patients among those who experienced malignant transformation. The most common subsite of malignant transformation was the tongue. The average time from diagnosis of OLP or OLL to transformation was 51.4 months.

Practical Implications. A small subset of patients with a diagnosis of OLP eventually developed SCC. The most common demographic characteristics of patients in this subset were similar to the most common demographic characteristics associated with OLP in general (that is, being female, being older and being affected in areas common to this condition). It is prudent for clinicians to pursue continued regular observation and follow-up in patients with these conditions, even in patients who do not fit a traditional high-risk category for oral SCC.

Key Words. Oral lichen planus; oral lichenoid mucositis; oral lichenoid lesion; squamous cell carcinoma; malignant transformation.

cases in terms of criteria used for the initial diagnosis of OLP. The investigators in many earlier case reports and studies presented cases that either involved no initial biopsy of the OLP lesion or had not been diagnosed according to described criteria. In 1978, the World Health Organization (WHO) developed diagnostic criteria for OLP that included both clinical and histopathological standards.\(^1\) By using defined criteria, investigators can produce studies that are more uniform and comparable because they clearly establish that the condition of interest (that is, OLP) was present at the onset of the study. In 2003, van der Meij and van der Waal\(^2\) proposed a modification of the WHO diagnostic criteria for OLP to include definition of an entity referred to as “oral lichenoid lesion” (OLL) and to differentiate between OLL and OLP clinically and histopathologically. In addition, this standard included “absence of epithelial dysplasia” in the histopathological criteria of OLP and OLL, in an attempt to exclude lesions termed “lichenoid dysplasia,” a term that refers to lesions with biopsy-proven epithelial dysplasia that also exhibit lichenoid features.

Our specific objective in this systematic review was to evaluate the literature (in the context of the most recently modified WHO diagnostic criteria for OLP and OLL,\(^4\) which by definition exclude cases with epithelial dysplasia) for the following characteristics: the prevalence of malignant transformation of OLP or OLL to SCC; the clinical situation in which malignant transformation most often occurs, including age, sex, location of the lesion and subcategory of OLP or OLL; and the range of time reported for malignant transformation. A secondary objective was to look for any evidence of a difference between OLP and OLL with regard to malignant transformation.

### METHODS

**Sources.** We searched the databases PubMed (1950-October 2012), Embase (1947-October 2012) and Thomson Reuters Web of Science (1965-October 2012) with the strategy listed in Table 1. We placed no limits on the searches. At the onset of the study, we searched the Cochrane Database of Systematic Reviews, but it yielded no relevant results. Therefore, we did not choose it as one of the selected databases for our search. One of the reviewers (S.G.F.) screened the identified publications according to title and abstract, and she then chose publications to obtain and evaluate in full-length versions against the inclusion criteria. The same reviewer repeated the search before we submitted the manuscript of this article in March 2013, and she and another author (S.C.G.) also evaluated late-breaking publications for inclusion.

**Selection process.** We required that included articles be full-length, English-language articles about studies involving human participants, published in peer-reviewed journals. Included studies were solely observational in nature, owing to the topic of interest, and were limited to cohort studies (prospective or retrospective) and large case series or record reviews that provided sufficient information regarding the overall group of patients with OLP or OLL. We excluded case-control studies because, although they were observational in nature, they could not provide sufficient information on the cases of OLP to yield a transformation rate and, thus, did not contribute to the goal of this review. We excluded individual case studies. We used scientific meeting abstracts identified through the search process to search for full-length publications, and we included them only if we found such a publication. If the study included both cases of OLP and cases of lichen planus confined to the skin, then we required that these cases be clearly defined and classified into separate groups by the original investigators for statistical and case description purposes. For a study to be included, we required that all cases of OLP or OLL in it have been proven by means of biopsy results at initial diagnosis, and we required that the study investigators have stated clearly that they had excluded from their study patients who had any form of epithelial dysplasia on initial diagnosis of OLP or OLL, so as to exclude from our study cases of so-called lichenoid dysplasia. If the study investigators stated that they had used the WHO guidelines modified in 2003 by van der Meij and van der Waal\(^2\) to confirm diagnosis of OLP or OLL in all included cases, we considered this sufficient evidence that cases

### TABLE 1

<table>
<thead>
<tr>
<th>DATABASE</th>
<th>KEY WORD (MeSH,* EMTREE) TERM AND TEXT WORD SEARCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embase</td>
<td>(“lichen planus” OR ‘lichen planus’:ab,ti OR ‘lichenoid’:ab,ti AND ‘(carcinoma)’ OR ‘(cell transformation)’ OR ‘(treatment outcome)’ OR ‘(precancer)’ OR ‘malignant”:ab,ti OR ‘cancer”:ab,ti OR ‘premalignant’:ab,ti OR ‘outcome’:ab,ti OR ‘disease progression’:ab,ti</td>
</tr>
<tr>
<td>Thomson Reuters Web of Science</td>
<td>(((“lichen planus”) OR (“lichenoid”)) AND (“squamous cell carcinoma”) OR (“carcinoma”) OR (“malignant”) OR (“transformation”) OR (“outcome”) OR (“premalignant”) OR (“progression”) OR (“cancer”))</td>
</tr>
</tbody>
</table>

* MeSH: Medical subject headings.
with dysplasia were excluded on initial diagnosis. Finally, we either eliminated repeat publications or evaluated them in the context of the included study, generally using the most recent publication. All reviewers agreed on the inclusion criteria, and one reviewer (S.G.F.) screened the full-length articles against the inclusion criteria.

Data extraction. We extracted data in two phases. First, we conducted an evaluation of the overall study itself, and then we evaluated every case of malignant transformation of OLP or OLL listed in each study, the results of which assessment we used for evaluation of the case characteristics. The complete data extraction forms are available in Appendix 1 in the supplemental data to the online version of this article (found at http://jada.ada.org/content/145/1/45/suppl/DC1).

Methodological quality assessment for risk of bias. The adaptation of an appropriate quality assessment tool for the types of articles included in this systematic review was a challenge. We adapted the Newcastle-Ottawa Scale for this study, as its use in the evaluation of systematic reviews of observational studies is established; however, the tool included only adaptations for case-control and...
cohort studies. We modified the cohort version to fit our systematic review format. No comparable ready-made quality assessment tool was available for the other group of studies (large case series or record reviews of the malignant transformation of OLP or OLL with sufficient background information regarding the overall group of patients initially diagnosed with OLP or OLL). Therefore, we modified the cohort version of the Newcastle-Ottawa Scale\(^7\) to suit these studies by eliminating question no. 2, which deals with selection of the nonexposed cohort. The modified Newcastle-Ottawa Scales for cohort studies and large case series and record reviews are available in Appendix 2 in the supplemental data to the online version of this article (found at http://jada.ada.org/content/145/1/45/suppl/DC1). The scales differed in total possible points by one point (nine for the cohort studies tool and eight for the large case series–record reviews tool), so we separated the studies for purposes of data analysis and discussion.

Two reviewers (S.G.F. and S.C.G.) independently reviewed each article in the systematic review, using whichever Newcastle-Ottawa quality assessment tool was available for the type of study included.

### TABLE 2

<table>
<thead>
<tr>
<th>STUDY</th>
<th>COUNTRY OF ORIGIN</th>
<th>TOTAL CASES OF OLP* OR OLL†</th>
<th>SUBTYPE OF LESIONS IN CASES OF OLP OR OLL, %</th>
<th>CASES OF SCC‡</th>
<th>MALIGNANT TRANSFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Red‡</td>
<td>White§</td>
<td>Mixed¶</td>
</tr>
<tr>
<td>Gümrü,(^9) 2013</td>
<td>Turkey</td>
<td>370 OLP</td>
<td>60.5</td>
<td>39.5</td>
<td>NA**</td>
</tr>
<tr>
<td>Bardelli and Colleagues,(^9) 2013</td>
<td>Italy</td>
<td>204 OLP</td>
<td>27</td>
<td>73</td>
<td>12.3</td>
</tr>
<tr>
<td>Kaplan and Colleagues,(^9) 2012</td>
<td>Israel</td>
<td>171 OLP</td>
<td>NA</td>
<td>NA</td>
<td>63.2</td>
</tr>
<tr>
<td>Bombeccari and Colleagues,(^9) 2011</td>
<td>Italy</td>
<td>327 OLP</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bermejo-Fenoll and Colleagues,(^9) 2010</td>
<td>Spain</td>
<td>550 OLP</td>
<td>65</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Torrente-Castells and Colleagues,(^9) 2010</td>
<td>Spain</td>
<td>65 OLP</td>
<td>34</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>Fang and Colleagues,(^9) 2009</td>
<td>China</td>
<td>2,119 OLP</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Carbone and Colleagues,(^9) 2009</td>
<td>Italy</td>
<td>808 OLP</td>
<td>41</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Lim and Colleagues,(^9) 2009</td>
<td>Malaysia</td>
<td>30 OLP</td>
<td>25.6</td>
<td>63</td>
<td>11.3</td>
</tr>
<tr>
<td>van der Meij and Colleagues,(^9) 2007</td>
<td>Netherlands</td>
<td>67 OLP, 125 OLL</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Laejendecker and Colleagues,(^9) 2005</td>
<td>Netherlands</td>
<td>200 OLP</td>
<td>54</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Xue and Colleagues,(^9) 2005</td>
<td>China</td>
<td>674 OLP</td>
<td>48.7</td>
<td>51.3</td>
<td>0</td>
</tr>
<tr>
<td>Rode and Kogoj-Rode,(^9) 2002</td>
<td>Slovenia</td>
<td>55 OLP</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Eisen,(^9) 2002</td>
<td>United States</td>
<td>723 OLP</td>
<td>63</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Rajentheran and Colleagues,(^9) 1999</td>
<td>United Kingdom</td>
<td>832 OLP</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Holmstrup and Colleagues,(^9) 1988</td>
<td>Denmark</td>
<td>611 OLP</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* OLP: Oral lichen planus.
† OLL: Oral lichenoid lesion.
‡ Red: Predominantly red in clinical appearance.
§ White: Predominantly white in clinical appearance.
¶ Mixed: Predominantly mixed red and white in clinical appearance.
# SCC: Squamous cell carcinoma.
** NA: Not available.
†† WHO: World Health Organization. Source: van der Meij and van der Waal.\(^4\)
‡‡ CIS: Carcinoma in situ.
§§ Source: Rad and colleagues.\(^5\)
appropriate for the study type. They also independently completed data extraction forms (the overall study data extraction form and an individual patient data extraction form). A third reviewer (S.A.H.) acted as arbitrator in the case of disagreement between the two initial reviewers. The reviews then were combined into a final assessment for each of the included studies.

**Summary measures and methods of analysis.** We chose qualitative reporting to summarize data for this systematic review because of the observational nature of the studies and the multiple variables we planned to evaluate in the review. We summarized individual points of interest across studies. We pooled and summarized the included cases of SCC regarding multiple demographic and clinical features.

**RESULTS**

**Study selection.** Initially, the PubMed search yielded a result of 1,945 records, the Embase search yielded 2,284 and Thomson Reuters Web of Science yielded 1,089. The figure shows details regarding the full flow of information, presented according to the PRISMA format. After screening of the title and abstract, the numbers of full-length papers for retrieval and evaluation that met the inclusion criteria were 62 from PubMed, 80 from Embase and 52 from Thomson Reuters Web of Science. We then removed from these records publications that were duplicated across databases, leaving 87 publications. We identified an additional eight articles by hand searching literature references. We added three late-breaking publications, so in the end we evaluated 98 full-length papers against the inclusion criteria.

A summary of the full-length articles excluded and the reasons for their exclusion appears in eTable 1 in the supplemental data to the online version of this article (found at http://jada.ada.org/content/145/1/45/suppl/DC1). We excluded one large series of articles involving a related cohort because the initial publications involving the cohort did not specifically exclude dysplasia in all cases of OLP on diagnosis. After we applied the inclusion criteria, 16 studies remained for inclusion in the systematic review.

**Study results.** Table 2 shows the characteristics of the studies included in this review. Overall, 7,806 cases of OLP and 125 cases of OLL were studied. Eighty-five cases of SCC (plus five cases of carcinoma in situ [CIS]) developed in patients with a previous diagnosis of OLP, and four cases of SCC arose in patients who previously had had a diagnosis of OLL. The range of rate of transformation was between 0 and 3.5 percent for OLP and was 3.2 percent for the one study in which investigators evaluated patients with OLL. The annual rate of transformation was calculated in three studies. This rate ranged from 0.36 to 0.69 percent in OLP and was 0.71 percent in the one study in which investigators evaluated patients with OLL. The average rate of transformation among all studies involving patients with OLP was 1.09 percent when patients with CIS were excluded and 1.14 percent when cases of CIS were added to the cases of SCC.

The annual rate of transformation was calculated in three studies. This rate ranged from 0.36 to 0.69 percent in OLP and was 0.71 percent in the one study in which investigators evaluated patients with OLL. The follow-up time was an average 83.44 months in the 10 studies that included reports of this information, and it ranged from 0 to 312 months.

The individual patient data for all of the studies that included reports of cases of SCC arising in patients with previous diagnosis of OLP or OLL are shown in eTable 2 in the supplemental data to the online version of this article (found at http://jada.ada.org/content/145/1/45/suppl/DC1). Sufficient information was provided for 88 patients to be included in this summary. The average age of the patients was 60.8 years (range, 30-89 years). Fifty-seven of the 87 patients who reported their sex were female (66 percent) and 30 were male (34 percent).
The most common locations in which transformation occurred were the tongue (51 percent of 88 cases reported, n = 45), followed by the buccal mucosa (32 percent of cases reported, n = 28). Of the tongue cases, 20 were in an unspecified subsite, 19 were on the lateral portion of the tongue, four were on the dorsal portion of the tongue and two were on the ventral portion of the tongue. The gingiva (11 percent, n = 10), lips (2 percent, n = 1 upper lip, 1 lower lip) and floor of the mouth (1 percent, n = 1) also were affected.

Table 3 presents a comparison of the demographic factors of age, sex and lesion subsite between the OLP-OLL overall study group, the patients within the OLP-OLL study group who also had SCC and the reference profile for patients with oral SCC. The average age of the patients with OLP or OLL and SCC was approximately 10 years older than that of the overall group of patients with OLP or OLL but was comparable with the overall average age of patients with oral cancer. Within the OLP-OLL group, the buccal mucosa was the subsite most frequently cited as having OLP or OLL, and a substantial percentage of cases of OLP or OLL with SCC also arose on the buccal mucosa, a site that is less frequently represented in oral SCC overall. The tongue represented a similar number of cases of OLP or OLL and of OLP or OLL with SCC, but the dorsal tongue subset of cases with OLP or OLL and SCC was at least two times greater than most estimates of the prevalence of overall oral dorsal tongue involvement in cases of SCC. Gingival involvement was common in the overall OLP-OLL group, but the gingiva was a less common site of SCC development in cases of OLP or OLL, considerably less than the overall rate of oral SCC-related gingival carcinoma. The floor of the mouth also appears underrepresented in patients with OLP or OLL and SCC cases as compared with its involvement in oral SCC overall.

Not all study investigators reported the subtype of OLP or OLL at the initial diagnosis, but among the studies that included this information, white variants were most common, followed by red and then mixed red and

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**TABLE 3**

Comparison of demographics between overall cases of OLP\* or OLL† in this study, cases of SCC‡ in this study and reference statistics for SCC in the oral cavity.§

<table>
<thead>
<tr>
<th>CLINICAL PARAMETER</th>
<th>OVERALL CASES OF OLP OR OLL IN THIS STUDY (N = 7,931)</th>
<th>CASES OF SCC IN THIS STUDY (N = 94, INCLUDING CASES INVOLVING CIS¶)</th>
<th>REFERENCE STATISTICS FOR ORAL CANCER (FROM SEER# DATA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age, Years</td>
<td>51.97 years (n = 7,069) 60.8 years (n = 87) 62 years</td>
<td>Estimated to be 3 to 5% of cases involving the tongue NA**</td>
<td>NA **</td>
</tr>
<tr>
<td>Sex, Percentage (No.)</td>
<td>Female 64 (n = 5,101/7,931) 66 (n = 51/87) 30</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Male 36 (n = 2,830/7,931) 34 (n = 30/87) 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Location, Percentage (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>Overall 53.18 (9 studies) 51 (n = 45/88) 40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Dorsal 36.44 (4 studies) 9 (n = 4/45) 35</td>
<td>Estimated to be 3 to 5% of cases involving the tongue</td>
<td>Estimated to be 3 to 5% of cases involving the tongue</td>
</tr>
<tr>
<td></td>
<td>Ventral and lateral 28.06 (4 studies) 47 (n = 21/45) 17</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Not otherwise specified NA 44 (n = 20/45)</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>Gingiva†† 44.33 (9 studies) 11 (n = 10/88)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>5.67 (9 studies) 1 (n = 1/88) 17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Lips</td>
<td>25.38 (3 studies)‡‡ 2 (n = 2/88)</td>
<td></td>
<td>2 (n = 2/88)</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>71.53 (10 studies) 32 (n = 28/88)</td>
<td></td>
<td>32 (n = 28/88)</td>
</tr>
<tr>
<td>Palate</td>
<td>7.98 (7 studies)§§ 7.98 (7 studies)§§</td>
<td></td>
<td>7.98 (7 studies)§§</td>
</tr>
<tr>
<td>Not otherwise specified NA NA 8</td>
<td></td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

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* OLP: Oral lichen planus.
† OLL: Oral lichenoid lesion.
‡ SCC: Squamous cell carcinoma.
§ Not all studies contained reports of each demographic item; therefore, individual items may be composed of less than the total number of patients in the study. Calculations were determined by means of weighted averages of each study’s results.
¶ CIS: Carcinoma in situ.
# SEER: Surveillance, Epidemiology, and End Results. Sources: National Cancer Institute,107 Rodu and Cole108 and Goldenberg and colleagues.109
** NA: Not available.
†† Gingiva including alveolar ridge mucosa.
‡‡ Of overall cases involving the lips, the lower lip was affected predominantly over the upper lip.
§§ Of overall cases involving the palate, the hard palate was affected predominantly over the soft palate.
white. Of the patients who developed SCC, 52 percent (n = 43) reported a red variant of OLP or OLL, 24 percent (n = 20) reported a white variant and 24 percent (n = 20) reported a mixed red and white variant (eTable 2 in the supplemental data to the online version of this article [found at http://jada.ada.org/content/145/1/45/suppl/DC1]). The average time from diagnosis of OLP or OLL to diagnosis of SCC (of the 81 cases for which this information was reported) was 51.4 months. Immunosuppressant conditions (most commonly diabetes mellitus and corticosteroid use) were reported in 13 cases, but not all studies included this information. The presence or absence of additional risk factors (specifically, tobacco or alcohol use) was reported in 79 cases: of these, 57 percent (n = 45) reported no history of tobacco or alcohol use, 22 percent (n = 17) reported history of or current tobacco and alcohol use, 14 percent (n = 11) reported history of or current tobacco use only, 5 percent (n = 4) reported history of or current alcohol use only and 3 percent (n = 2) specified no history of or current tobacco use but did not mention alcohol consumption (eTable 2 in the supplemental data to the online version of this article [found at http://jada.ada.org/content/145/1/45/suppl/DC1]).

Risk of bias and quality assessment of studies. Within-studies assessment. Tables 4,7,9,18,20,21,25,106 and 5,7,9-19,31-33,98,105 show the modified Newcastle-Ottawa (risk of bias) scores for the cohort studies and the case series studies included in this review. According to this scoring system, factors that influenced bias among the studies are separated into selection, comparability and outcome factors. In the selection category, factors lending higher credibility to the studies included OLP or OLL patients’ coming from a representative population in the community, nonexposed cohort participants’ being drawn from the same community (cohort studies only), ascertainment of exposure consisting of biopsy-proven cases (with a higher credibility given to studies with biopsy-proven cases according to the most recent set of criteria for OLP or OLL diagnosis) and demonstration that no dysplasia or SCC was present within the initial group of patients. In the comparability category, the factors we used to assess the credibility of these studies were control of secondary risk factors such as tobacco use and separation or differentiation of cases of OLL from cases of OLP (by controlling for cases that had a clear association with restorations and medications). Finally, in the outcome factor, we considered studies more reliable if they demonstrated stringent assessment of outcome, follow-up over five years and adequate number of study participants completing follow-up.

Across-studies assessment. When evaluating risk of bias across studies, one must consider the possibility of a publication bias toward studies in which investigators reported malignant transformation.Investigators in two studies included in this review did not find any cases of transformation to SCC.99,103 Another factor is bias associated with the relative scarcity of studies of only low-risk, low-symptom subtypes of OLP (although within these studies, white variants were quite common). Inconsistencies associated with self-reporting of risk factors by individual patients may introduce bias. Finally, because the length of follow-up periods varies within studies, assessment of the true risk of malignant transformation may be skewed when one compares cases that have been followed for differing periods.

DISCUSSION

Summary of evidence. The results of this review revealed that—despite our having limited the included studies to those in which the researchers excluded patients with OLP or OLL cases with dysplasia at onset—a small subset of patients with diagnoses of OLP eventually developed SCC. The average rate and range of malignant transformation found in this review is lower and narrower than those included in prior reviews.14 The most common demographic characteristics of patients with OLP are female sex and, on average, being in the sixth decade of life.20 OLP has been reported to affect the buccal mucosa most commonly, followed by the lateral tongue and gingiva, although in our study the OLP-OLL group findings revealed the dorsal tongue to be affected more commonly than the lateral tongue.26 The most common presentation of patients with SCC in this study included a demographic profile strikingly similar to that of patients with OLP in general in regard to female sex, age and location of disease involvement.

Owing to the availability of only one study in which investigators differentiated between OLP and OLL, the data are insufficient at this time to determine whether the rate of transformation of these two types of oral lichenoid mucositis differs.106 In addition, although researchers in several of the studies that included cases of OLP did attempt to exclude OLL cases by omitting cases that immediately could be associated with restorations or medications (studies in which investigators controlled for OLL confounding variables can be seen in Tables 4,7,9,18,20,21,25,106 and 5,7,9-19,31-33,98,105), it is probable that these two groups cannot be separated reliably for the purposes of the overall review.

Limitations. Several limitations may affect the conclusions of this study. First, available resources did not permit a systematic review that included articles written in all languages; therefore, the study was limited to English-language articles. Of the initial records identified by means of the database searches, approximately one-fifth were written in languages other than English. In addition, the use of only one reviewer for the initial screening in our study may have resulted in increased bias in the study selection process.

Another overall limitation of a review of this nature is the inherent difficulty in aggregating data that depend
on initial diagnoses impossible to verify independently, especially the presence or absence on initial biopsy of any type of premalignant change. According to the criteria we used in this article, only epithelial dysplasia on initial diagnosis of OLP or OLL was an exclusionary condition, and the initial presence or absence of epithelial atypia was not reported by the authors of the included studies. It is likely that some of the patients included in this study may have exhibited atypia on initial diagnosis, thus introducing bias to the results. This is a point of controversy, however; it has been suggested that eliminating cases with dysplasia on initial biopsy may lead to a falsely low rate of true malignant transformation of OLP—because if OLP truly is a potentially premalignant disorder, dysplasia may represent a valid stage in the development of SCC.

Variability between practitioners’ evaluations of clinical and histopathological diagnosis standards, even when the clinicians are following a set of accepted criteria, also may lead to difficulty in accurately as-

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<td><em><em>Modified Newcastle-Ottawa Scale</em> scoring for cohort studies.†</em>*</td>
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<td>Bombeccari and Colleagues, 2011</td>
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<td>Carbone and Colleagues, 2009</td>
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<td>van der Meij and Colleagues, 2007</td>
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<td>Laejendecker and Colleagues, 2005</td>
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<td>Rajentheran and Colleagues, 1999</td>
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<td>Holmstrup and Colleagues, 1988</td>
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* Based on the original Newcastle-Ottawa Scale by Wells and colleagues. 7
† A blank cell indicates that the study did not meet the criterion and thus did not earn a point for it.
‡ OLL: Oral lichenoid lesion.
§ Total possible score: 9.

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<td><em><em>Modified Newcastle-Ottawa Scale</em> scoring for large case series.†</em>*</td>
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<td>Gümrü, 2013</td>
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<td>Bardellini and Colleagues, 2013</td>
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<td>Kaplan and Colleagues, 2012</td>
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<td>Bermejo-Fenoll and Colleagues, 2010</td>
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<td>Torrente-Castells and Colleagues, 2010</td>
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<td>Xue and Colleagues, 2005</td>
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<td>Rode and Kogoj-Rode, 2002</td>
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<td>Eisen, 2002</td>
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* Based on the original Newcastle-Ottawa Scale by Wells and colleagues. 7
† A blank cell indicates that the study did not meet the criterion and thus did not earn a point for it.
‡ OLL: Oral lichenoid lesion.
§ Total possible score: 8.
sessing the risk factors contributing to any given form of oral lichenoid mucositis. In addition, the location of the SCC in relation to the original areas affected by OLP or OLL also was not reported reliably in all of the studies, leaving open the possibility that some of the SCC may have arisen in areas previously unaffected by lichenoid disease.

It may not be possible to fully separate confounding factors such as concurrent risk factors for oral SCC (tobacco, alcohol use) from the risk represented by a diagnosis of OLP or OLL, especially because there is no accepted standard across studies about whether there should be strict exclusion of patients with other risk factors. Although investigators in several studies in this review recorded secondary risk factors, investigators rarely stated specifically either that they excluded from the study any patients with a history of or current tobacco or alcohol use or that they had controlled for these factors statistically in the outcome. It has been reported that approximately 75 percent of oral and pharyngeal cancers in the United States are related to tobacco and alcohol consumption. In our review, more than one-half of the patients with OLP or OLL and SCC did not report a history of tobacco or alcohol use.

An investigator calculating the rate of transformation also needs to consider significant discrepancies between studies. Most of the researchers in the large case-series studies calculated their rate of transformation via a simple average rate, but many of the cohort study investigators also were able to calculate annual rates of transformation on the basis of the length of time patients were followed up. Owing to this variability, in the overall systematic review we used the lowest common denominator method of calculating cases transforming to malignancy. However, this also may have led to bias in interpreting the results because this method does not take into account the time frame to transformation.

**Possible mechanisms of malignant transformation.**
Mechanisms that explain malignant transformation in OLP have been proposed in the literature. One is based on the concept that the inflammatory infiltrate causes oxidative stress and leads to the release of inflammatory cytokines, which then activate transcription factors in premalignant cells. This hypothesis is similar to those explaining other types of chronic inflammatory diseases linked to cancer—for example, the increased risk of developing colorectal carcinoma in patients with chronic inflammatory bowel disease. A detailed exploration of these mechanisms is beyond the scope of this article.

**CONCLUSIONS**

In this study, we found a low rate of SCC occurrence in patients with OLP or OLL when we included only studies of the malignant transformation of OLP or OLL in which researchers used current diagnostic criteria and excluded patients who had dysplasia on initial diagnosis. Patients who experienced malignant transformation followed a classic OLP demographic in terms of age, sex and oral subsite of involvement, and these data confirmed prior findings that erythematous or ulcerated forms of the condition are associated with a higher risk of malignancy. However, the patients who experienced malignant transformation differed from patients with conventional SCC in terms of sex and site. Insufficient evidence exists at this time to determine whether there are differences regarding risk of malignant transformation between OLP and OLL.

It still is unclear whether a patient with OLP has an independent risk of experiencing malignant transforma-
tion to SCC, or whether areas of oral epithelium with a premalignant potential—perhaps even areas with molecular changes manifesting clinically as normal or histologically with unrecognized atypia that is not yet dysplasia—evolve a nonspecific “lichenoid response” that causes them to enter the inflammation–carcinogenesis loop. In such a loop, inflammatory cells might promote malignant transformation in the epithelial cells. Helpful to resolving this issue would be additional large studies in which investigators differentiate carefully between OLP and OLL, exclude participants who have dysplasia at the time of OLP or OLL diagnosis and specifically state whether patients have other established risk factors for SCC. Ideally, if the possible premalignant potential of OLP or OLL could be assessed via molecular study before dysplasia develops, it could separate cases that may progress to SCC from those that may have limited potential for transformation, allowing a more accurate characterization of the risk potential in each of these groups.

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