

***Evidence-Based Approach Literature Evaluation: Is Oral Lichen Planus  
Premalignant?***

Evidence-Based Care Module

Community Dentistry 300Y

March 9, 2006

Elyse Axelrod, Kenneth Lee, Mindy Fong, Sean Ostro, and Ray Shin

## ***Abstract***

This evidence-based review of the literature examines the possibility of a premalignant relationship between Oral lichen planus (OLP) and Oral squamous cell carcinoma (OSCC). The results were based on an electronic search of various databases. The 94 articles obtained were assessed based on a determination of relevance inclusion criteria. This yielded four articles that were scored against a checklist for assessing causation. From the articles scored, there was insufficient evidence to conclude about the potentially premalignant nature of OLP. Further research in this area is required to make a recommendation to clinicians.

## ***Introduction***

Oral lichen planus (OLP) is a chronic condition commonly found on the buccal mucosa, tongue, gingiva, labial mucosa, and lower lip of the oral cavity.<sup>1</sup> It is characterized by hyperkeratosis and epithelial thinning, and histological sections show rete ridges and the destruction of basal keratinocytes.<sup>2</sup> The most common forms, listed in increasing severity, are reticular, erosive, and ulcerative. The prevalence of this condition is 1-5% of the general population, affecting women twice as often as men. It occurs mostly in the 40 to 50 age group and is relatively rare in children.<sup>1,3</sup>

Many previous studies have focused on whether OLP is a premalignant condition.<sup>3-7</sup> Many authors have examined the number of malignant cases arising from a population with confirmed Oral Lichen Planus. Generally, evidence supporting the premalignant nature of OLP is limited and previous reviews were inconclusive.<sup>3,5-8</sup>

A systematic review of the literature was used to examine whether or not oral lichen planus is pre-malignant. This report explains the search strategy as well as the strongest evidence to answer this question.

## ***Methods***

### **Search Strategy**

Electronic databases were searched using several key words: oral lichen planus, precancerous, premalignant, carcinoma, malignant, malignancy, oral lichenoid lesions and oral lichen. The databases searched were PubMed (1966-present), Ovid Medline (1950-present), Scopus (1966-present), Medical & Pharmaceutical Biotechnology Abstracts (1993-present), and ISI Web of Knowledge (1990-present). These searches yielded 84, 62, 59, 45 and 32 potentially relevant articles, respectively. The search results were limited to studies in English and studies on humans. A total of 282 articles were obtained.

### **Determination of Relevance**

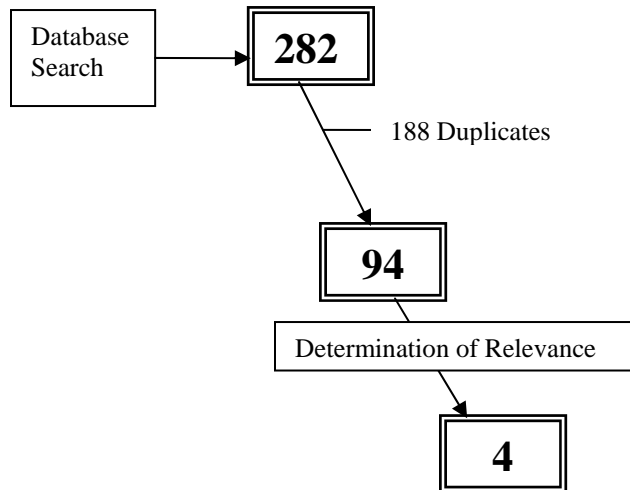
After elimination of 188 duplicate articles, 94 articles remained. An inclusion criteria consisting of five items was applied to the title of the articles, to determine which articles were relevant to this assessment (Table 1.) Articles that met all five criteria were deemed relevant. First, the study conducted must have been primary research. All review articles, editorials, commentaries, articles related to the management of the condition, and the clinical diagnosis of the condition

were excluded. Secondly, OLP had to be examined as a specific risk factor for malignant transformation. Any studies which looked at OLP in conjunction with other confounding factors were not included in this study. Thirdly, articles were excluded based on study design. Only cohort, case-control, or cross sectional studies were included. Although ideal for causation studies, randomized control trials are basically impossible to employ in this case. For the fourth criterion, the odds ratio must have been reported or could be calculated from the study. Finally, the articles had to be accessible to University of Toronto students.

**Table 1: Determination of Relevance.** Articles that met all five inclusion criteria were deemed relevant.

- |  |
|--|
| <ol style="list-style-type: none"><li>1) The article must be primary research</li><li>2) OLP assessed as a specific risk factor</li><li>3) Cohort, Case-control, or Cross sectional study design</li><li>4) Odds Ratio reported or could be calculated</li><li>5) Articles accessible to U of T students</li></ol> |
|--|

Of the 94 articles examined, only four met all five inclusion criteria (Figure 1). The reference lists from these articles were examined in order to obtain additional articles. Five new articles were found using this method; however, none met the original inclusion criteria.



**Figure 1.** Initial search yielded 282 articles. With elimination of duplicate articles and studies that did not meet the five determination of relevance criteria (see Table 1), the number was narrowed down to four.

## Validity Instrument

The four articles deemed relevant were then scored according to a checklist for assessing causation. This checklist consisted of five general questions related to causation and eight questions of causation related to non-infectious agents (Table 2.) The highest possible score was 13.

**Table 2: Checklist for assessing causation for each relevant article.**<sup>9</sup>

General questions
1) Was the study ethical?
2) Was a strong design used to assess causation or risk?
3) Were the cases validly defined and reliably measured?
4) Were the risks validly defined and reliably measured?
5) For diseases with multifactorial risks, did the assessment of risks control for potential confounding factors, and did the model have strong power of prediction?
6) Questions about <b>causation</b> related to non-infectious agents
A) Did the purported cause precede the effect?
B) Was the estimate of risk beyond chance, and was it large?
C) Was there a dose-dependent relationship?
D) Was reversibility demonstrated?
E) Was the purported cause consistently observed in different times and places?
F) Is the purported cause biologically plausible?
G) Is the purported cause specific to that disease?
H) Is the purported cause analogous to another established disease or exposure?

## Results

Of the four relevant studies, the highest score obtained was seven out of the maximum 13. Therefore, none were considered to present strong evidence (Table 3). The fourth study was excluded for reasons explained below.

The first study scored was a retrospective cohort study which compared the prevalence of squamous cell carcinoma in a treatment group of 200 OLP patients to the prevalence in the general European population.<sup>4</sup> They presented an odds ratio of 12.5 that was not statistically significant. Many external factors existed with the study that did not allow the researchers to conclude whether OLP was intrinsically pre-malignant. While there was an attempt to control for some potentially carcinogenic factors, the control was not complete. Certain factors such as usage of topical corticosteroids and concomitant diseases were not controlled. As well, there was uncertainty in the initial diagnosis of OLP as inter- and intra-observer variations may have influenced the results, despite using the World Health Organization (WHO) criteria for OLP diagnosis.<sup>4</sup> Furthermore, only seven patients out of 200 were followed up with biopsy sections and thus malignancies which may have been present in the remaining 193 patients were possibly overlooked.

The second study compared biopsies of OLP to biopsies of general chronic inflammation, by grading their degree of epithelial dysplasia. All were taken from a pre-existing bank of histological sections at Harvard School of Medicine, Boston.<sup>5</sup> Dysplasia, as opposed to Squamous Cell Carcinoma, was scored as none, mild, moderate, or severe. Comparing those

sections with dysplasia (mild, moderate, or severe) to those with none, an odds ratio of 2.9 was calculated, which indicates a strong association between OLP and malignancy. However, confounding factors such as underlying disease, patient habits, and diet were not controlled for as the histological sections were taken from a bank without such information. Although the study did not control for confounding factors, the use of histological sections to compare those patients with OLP and those with chronic inflammation presents a stronger case as histological verification is the gold standard of OLP diagnosis.<sup>2</sup>

A third study examined a population of patients diagnosed with OLP at Goteborg University in Sweden, and then identified the number of patients who matched up in the Swedish Cancer Registry with OSCC.<sup>6</sup> The general population was used as a control, though the actual estimates were not reported, and thus the results could not be recalculated. Out of the patients diagnosed with OLP, only 62% of the diagnoses were confirmed using histological examination of the biopsy specimen, while the others were made based on clinical criteria, which could vary subjectively by the examiner. The observed incidence of OSCC in the study group was higher than the expected incidence, with a statistically significant odds ratio of 20. However, this odds ratio is unfounded due to the ambiguity and deficiency in the data reported. There were originally eight cases in the cancer registry of people previously diagnosed with OLP, but two were excluded as they were registered with both diagnoses less than three months apart, and a further case was excluded in the analysis based on insufficient information regarding the onset of OLP. In one of the five cases that remained, the OSCC appeared in an area of the mouth other than where the OLP was reported, though it was still included in the analysis. All five relevant cases were histopathologically verified. The study also examined incidences of other malignancies outside of the oral cavity in these patients, and there were no statistically significant findings or correlations with OLP. There were no controls for other confounding variables in this study, nor was there enough information recorded in these registries to further investigate the details of the findings. Though the results showed to be statistically significant confirming the relation between OLP and OSCC, the accuracy in the methods used to determine this are questionable.

One other study focused on comparing the premalignant potential between OLP and Oral Lichen Lesions to the general Dutch population.<sup>7</sup> The result from each study group was compared to the rate obtained with a similar demographic group within the Dutch population. The data provided did not permit accurate determination of the strength of the risk measure; therefore, the study was discounted.

## ***Discussion***

The characteristics of OLP satisfy the criteria set out by the WHO as having premalignant potential. However, there is much controversy in determining the association between OLP and OSCC. There are many factors that limit the strength of the evidence in these studies. The initial diagnosis of OLP is difficult; diagnosis between clinicians can vary, especially because many characteristics of OLP are similar to differentially diagnosing lesions.

In addition, the size, type, number, and frequency of lesions are not often addressed and thus the nature of the lesions is somewhat ambiguous. This leaves a wide margin for variation within the

patient population diagnosed with OLP. In addition, it is not yet understood if OLP can stimulate adjacent non-lesion containing sites in developing cancer.

The presence of confounding variables is difficult to control for – especially smoking. Even if studies excluded subjects that were currently practicing such habits, any previous history could also contribute to the decline in accuracy of the results.

Patients in many of these study groups were those going to seek medical opinions from specialists, which may suggest that the sample is taken from a population with lesions that have already progressed into the clinically more severe stages and subtypes of OLP.

Furthermore, the treatment of OLP with either topical or systemic corticosteroid therapy can possibly influence the progress of the lesion to a cancerous form. Differentiating between steroid treated versus non-treated may not be practical, as the prevalence of OLP stated in the current literature is low; hence, obtaining an adequately large test population would consequently be difficult. Along with limitations in population size, the lengths of the cohort periods are typically too short to obtain statistically significant results.

The design of future research studies need to shy away from the common flaws found within the majority of the present literature. Implementation of better strategies for identifying causation will help alleviate the uncertainty behind this long-standing debate. The following are recommendations for stronger study designs:

- Application of strict, well defined diagnostic criteria
- Larger sample size population
- Controls for confounding variables such as smoking
- Calibrating diagnostic assessment by clinician
- Employing strong study design for determination of causation
- Comparing the test results with control groups for oral cancer

There is not enough reliable evidence at present to supply much relief to the long debated issue of the precancerous nature of OLP. Stronger, more conclusive studies are required in order to reduce the ambiguity and improve the confidence of the clinician when treating patients with OLP, and before any firm recommendations can be made.

**Table 3: Premalignant nature of oral lichen planus**

AUTHORS, STUDY DESIGN, AND SCORE	POPULATION	PREVALENCE OF OSCC	VARIABLES INVESTIGATED	TYPE OF DENTAL EXAMINATION AND RELIABILITY	DEFINITION OF CONDITION RECORDED	CHARACTERISTICS OF OLP RECORDED	CONTROL OF CONFOUNDING VARIABLES	ODDS RATIO AND CONCLUSIONS
Laeijenderker and others (Retrospective Cohort Study) Score 7/13	Patients older than 18 years of age, with histopathological diagnosis of OLP and without an atypical dysplasia/malignant features or oral malignancy in the past between 1991-1993 in Rotterdam, the Netherlands (n=200)	1.5% (3 out of 200 Caucasian Patients Studied)  0.004% in Europe	Sex, Age, Clinical Variant of OLP, Affected Anatomical Site, Duration of Disease, Prior immunosuppressive tx, exposure to potential carcinogens, other concomitant diseases	Further histopathological examination on a yearly basis of OLP patients if clinical suspicion of malignancy was suspected i.e. progression of lesions, external or aggravating factors risk factors	SCC development in same site as OLP based on histopathological examination (essential features: invasion thru basement membrane and epithelial dysplasia)	Hyperkeratotic Variant of OLP Erosive or Ulcerative Variant of OLP Atrophic or Erythematous Variant of OLP Location of OLP listed in diminishing frequency (buccal mucosa (symmetrical), lateral margins of tongue, the gingiva, the labial mucosa, dorsal part of tongue, palate, floor of mouth)	Study tried to control smoking and systemic corticosteroid use as confounding variables by eliminating such cases based on criteria for acceptance of OLP undergoing malignant transformation	Statistical Analysis based on 4 oral malignancies per 100000 individuals/year in Europe vs 3 cases of SCC of 2000 person years in this study Probability of 3 case of SCC is $p=0.00008$ (Poisson distribution) Statistically significant figure OR = 37.5 Intrinsic malignant of OLP causing SCC 1 case ( $p=0.08$ (Poisson distribution) Not statistically significant OR = 12.5
Odukoya and others (Retrospective Cohort Study) Score 6/13	Patients 18-84 years old (mean=55) with histological diagnosis of OLP. Control population comparable in age and sex with study group. Histological sections of chronic inflammation taken from Harvard School of Medicine, Boston (study n=100, control n=100)	Study measured dysplasia. Prevalence of dysplasia in study group = 11% Prevalence of dysplasia in control group = 10%	Sex differences, lesion variation, and lesion location	Histological sections were retrieved from a bank of patients with confirmed OLP and a control group with chronic inflammation. Dysplasia was scored according to stringent criteria set by the researchers	Three stages of dysplasia were measured by studying sections and following stringent criteria as defined by the researchers	Irregular epithelial stratification, hyperplasia of the basal layer, drop-shaped rete ridges, increased number of mitotic figures	Histological slides of patients with chronic inflammation	OR = 2.9. Study did not control for confounding factors such as underlying disease, smoking habits, or use of corticosteroids. Data shows there is little difference between study group and control group. Further research with more stringent controls for confounding factors is needed
Rodstrom and others (Retrospective Cohort Study) Score 6/13	Patients 18-86 years old (mean=55), 677 female, 351 male, diagnosed with OLP at Goteborg University, Sweden, between 1978 and 1993 (n=1028)	0.49%	Malignant transformation rate, survival	Histopathological examination of biopsy specimens (n=635) and clinical criteria (n=393)	Oral Lichen Planus defined according to WHO diagnostic criteria; Oral Squamous Cell Carcinoma as registered in the Swedish Cancer Register based on ICD version 7 and updated with versions 8 and 9	OLP lesions were all erythematous or ulcerative type and located in the buccal mucosa, gingiva, or floor of the mouth	No control for confounding variables	Observed incidence of Oral Squamous Cell Carcinoma was higher than the expected incidence in the study group (statistically significant $P<0.001$ ) OR=20 (95% CI 6.5-46.7) though unable to confirm based on lack of raw data reported

## ***Works Cited***

1. Dissemond J. Oral lichen planus: an overview. *J Dermatolog Treat* 2004; 15(3):136-40.
2. Meeting of Investigators on the Histological Definition of Precancerous Lesions. In Geneva: World Health Organization, 1972.
3. Eisen D, Carrozzo M, Bagen Sebatien JV, Thornsprasom K. Oral lichen planus: clinical features and management. *Oral Dis* 2005; 11(6): 338-49.
4. Laeijendecker R, van Joost T, Kuizinga MC, Tank B, Neumann HA. Premalignant Nature of Oral Lichen Planus. *Acta Derm Venereol* 2005; 85(6):516-20.
5. Odukoya O, Gallagher G, Shklar G. A Histologic Study of Epithelial Dysplasia in Oral Lichen Planus. *Arch Dermatol* 1985; 121(9):1132-6.
6. Rodstrom PO, Jontell M, Mattsson U, Holmberg E. Cancer and oral lichen planus in a Swedish population. *Oral Oncol* 2004; 40(2):131-8.
7. Van der Meij E, Schepman K, Van der Waal I. The possible premalignant characterer of oral lichen planus and oral lichenoid lesions: A prospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96(2):164-171.
8. Zakrzewska JM, Chan ES, Thornhill MH. A systematic review of placebo-controlled randomized clinical trials of treatments used in oral lichen planus. *Br J Dermatol* 2005; 153(2):336-41.
9. Leake JL, Dept of Biological and Diagnosic Sciences, Faculty of Dentistry, University of Toronto. Unpublished document. Course notes DENT 1040Y 2001.
10. Larsson A, Warfvinge G. Oral lichenoid contact reactions may occasionally transform into malignancy. *Eur J Cancer Prev* 2005; 14(6):525-9.