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Original Article

# Malignant transformation of Taiwanese patients with oral leukoplakia: A nationwide population-based retrospective cohort study

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Cohort study;
Taiwan

*Background/Purpose:* Oral leukoplakia (OL) is one of the clinically diagnosed oral potentially malignant disorders (OPMDs) with an increased risk of oral cancer development. In this study, we investigated the malignant transformation of OL in Taiwanese population.
*Methods:* A retrospective cohort study was analyzed from Taiwan's National Health Insurance Research Database. A comparison cohort was randomly frequency-matched with the OL cohort according to age, sex, and index year. Oral submucous fibrosis (OSF) and oral lichen planus (OLP) were further stratified to evaluate the possible synergistic effects for OL-associated malignant transformation.
*Results:* In this cohort, 102 (5.374%) of 1898 OL patients were observed to transform into oral cancer. The malignant transformation rate was 26.40-fold in the OL cohort than in the comparison cohort after adjustment (95% confidence intervals 18.46–37.77). To further stratify with OSF and OLP, OL with OSF (58.38; 95% confidence intervals 34.61–98.50) and OL with OLP (36.88; 95% confidence intervals 8.90–152.78) had higher risk of malignant transformation rate than OL alone (27.01; 95% confidence intervals 18.91–38.59). The Kaplan–Meier plot revealed the free of malignant transformation rate was significant over the 13 years follow-up period (log-rank test, $p < 0.001$).
*Conclusion:* OL patients exhibited a significantly higher risk of malignant transformation than those without OL. In addition, both OSF and OLP could enhance malignant transformation in

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patients with OL. However, further studies are required to identify the histopathological and clinical parameters in the pathogenesis of malignant transformation among OPMDs.


## Introduction

Oral leukoplakia (OL) is an asymptomatic and the most commonly encountered entity in clinical practice. The estimated prevalence rate of leukoplakia is 2% worldwide.[1] The lesions of OL present particularly in the mouth floor, tongue, lip, and vermilion. Histopathologically, OL shows such as epithelial hyperplasia, hyperkeratosis, and/or hyperparakeratosis, with or without epithelial dysplasia or carcinoma. Clinically, OL is a diagnosed pre-neoplastic lesion of the oral cavity with a frequency of malignant transformation from 3.73 to 29%.[2–5]

Oral cancer is one the leading causes of cancer mortality worldwide, and early diagnosis of high risk, potentially malignant lesions are the higher priorities for the reduction of morbidity as well as mortality.[6–8] The fact that oral cancer could occur from OL, which is clinically easily accessible, early detection of high-risk lesions, and to conduct chemoprevention trials for arresting or removing the lesions. Early detection of a malignancy, especially in the pre-malignant stage, can significantly decrease the mortality and morbidity.[9]

In this study, we investigated the retrospective cohort study using the latest version of Taiwanese National Health Insurance Research Database (NHIRD) to evaluate the rate and time to malignant transformation of OL in nationwide population. In addition, the oral potentially malignant disorders (OPMDs) including oral submucous fibrosis (OSF) and oral lichen planus (OLP) were further stratified to evaluate the possible synergistic effect in the malignant transformation of OL.

## Materials and methods

### Data sources

Taiwan's National Health Insurance is a single-payer national program launched in 1995, this insurance program has provided health care up to 99.9% of whole population in 2014.[10] The records of the number of cases, treatment patterns, and medical claims reported for reimbursements are reformatted and maintained as NHIRD. The Longitudinal Health Insurance Database 2010 (LHID2010) was used for this cohort study with the approval from Institutional Review Board at the Chung Shan Medical University Hospital. The International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) was used to identify the patients' diseases. The demographic data, dates of clinical visits, diagnostic codes, prescription details, expenditures, and registration files were included in the data subsets. These high quality databases have previously been used for epidemiologic researches and the associations of diseases.[11–15]

### Study population

We identified ambulatory patients for dental visit with newly diagnosed OL (ICD-9-CM code: 528.6) from 2001 to 2012 as the OL group, with the date of OL diagnosis being defined as the index date. Those with a history of oral cancer (ICD-9-CM codes: 140-149) before the index date or follow-up $\leq$1 year were excluded. The non-OL cohort patients were randomly identified from the LHID2000 during the same period, without a history of OL at a ratio of 1:52 and frequency matched based on age (at 5-year intervals), sex, and index year with the patients in the OL group. The patients with age younger than 18 years old or age older than 65 years old were withdrew from program. The exclusion criteria were the same for both groups. The OPMDs with specific ICD-9-CM code OSF (codes: 528.8) and OLP (codes: 697.0) simultaneously diagnosed with OL were further evaluated for the possible effects of OL-associated malignant transformation.

### Outcome and comorbidities

The main outcome of this study was newly diagnosed oral cancer during follow-up. The patients were followed from the index date until oral cancer diagnosed, withdrawal from the insurance system, death, or December 31, 2013, which ever occurred first. A Charlson comorbidity index (CCI) derived for each individual in the cohort diagnosed before the index date was analyzed. The Charlson score was categorized as: 0, 1, and $\geq$2 with higher scores indicating greater comorbidity.[16]

### Statistical analysis

Demographic factors including age, sex, and comorbidities were compared between the 2 groups. Chi-squared tests were used to examine differences in the sex and comorbidity distributions. Student's t-tests were used to examine differences of mean age between the 2 groups. The hazard ratios (HRs) of oral cancer (ICD-9-CM code: 140-149) were calculated using Cox's proportional hazard regression analysis. In multivariable Cox's regression analyses, the HRs were presented with 95% confidence intervals (CIs) after controlling variables with a significant difference in crude model. The statistically significant level was set at p value $<$0.05. All statistical analyses were performed with the SPSS version 19 (SPSS, Chicago, IL, USA).

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