Objectives. The objectives of this study were to investigate the incidence of oral squamous cell carcinoma (OSCC) developing in lesions that were previously diagnosed as oral lichen planus (OLP), and to evaluate potential contributing factors that might be associated with an increased risk for the development of OSCC in these patients.

Study design. We retrospectively reviewed a relatively large cohort of 518 patients with OLP who received long-term follow-up (range, 6 months-21.5 years).

Results. There were 353 females and 165 males. Of these, 5 (0.96%) patients developed OSCC with a mean duration of 70 months. All were females with no history of smoking or alcohol use. Four of them received corticosteroid therapy. Notably, 1 of these patients received systemic corticosteroid therapy 13 months before transformation, and died of metastatic disease 46 months after transformation.

Conclusions. The incidence of OSCC developing in lesions previously diagnosed as OLP is less than 1%, and females were more commonly affected. These cases appear to represent the transformation of OLP into OSCC, however it cannot be entirely ruled out that these cases may represent de novo OSCC. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:592-596)

Oral lichen planus (OLP) is a relatively common inflammatory mucocutaneous disorder of unknown etiology. It has a protracted clinical course despite various available treatments.1,2 The age of onset is generally between the fourth and sixth decades and there is a sex predilection with a female: male ratio of 1.5–3.0:1.0.3-8 Reticular, papular, plaquelike, bullous, atrophic, and erosive are the terms use to describe the 6 distinct clinical forms of OLP that have been identified.9 Each of these clinical forms of OLP may occur as the only form of OLP seen in a patient, or concurrently with one or more of the other forms of OLP.9 Genital and cutaneous lichen planus are associated with approximately 20% and 15% of OLP, respectively.1

One of the most important issues concerning the progression and prognosis of OLP is the question of its potential for malignant transformation into oral squamous cell carcinoma (OSCC). Since 1910, when the first case of OSCC in a patient with OLP was reported,10 a number of studies have attempted to resolve this issue. In the latest review, Gonzalez-Moles et al.11 assessed the important studies of patients with OLP published between 1924 and 2007, and reported the frequency of malignant transformation as 0% to 12.5%. In the past decade, several high-quality studies revealed a frequency of 0.8% to 6.4%, with a follow-up period of 6 months to 16 years (mean >4 years).3-7 These findings generally support the hypothesis that patients with OLP carry a significantly increased risk of developing OSCC. As a result, the World Health Organization (WHO) classified OLP as a potentially malignant disorder.12

Nonetheless, the issue as to the potentially malignant nature of OLP is still controversial in the literature.11,13,14 This is partly because of variability in patient selection, differences in the criteria of OLP and its malignant transformation, time of follow-up, and information on exposure to the potential carcinogens and risk factors for oral cancer development. In addition, because immnosuppressive treatment may theoreti-cally increase the chances of developing OSCC,5 pre-
cise details of any potentially immunosuppressive treatment in patients with OLP (such as the use of corticosteroids) needs to be analyzed when investigating the question of its ability to undergo malignant transformation.

The objective of this retrospective study was to investigate the number of cases of OSCC developing in lesions that were previously diagnosed as OLP in 518 patients in an eastern China cohort, and to evaluate potential contributing factors that might be associated with an increased risk for the development of OSCC in these patients.

MATERIAL AND METHODS

All archived files of patients with the clinical and pathologic diagnosis of OLP in the Department of Oral Mucosal Diseases, Shanghai Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine, from 1978 to 2009 were retrospectively reviewed. In our clinic, periodic follow-up examinations at intervals of every 6 months (or less) were recommended for patients diagnosed with OLP. Telephone interviews were conducted to supplement the review. Histopathologic diagnoses of OLP were made by oral pathologists on duty from the Department of Oral Pathology, Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine. As previously mentioned,8 the WHO criteria (1978) for OLP15 were used when examining the histopathology of the sections. The exclusion criteria were as follows:

(1) Any patient with a clinical history and histopathologic changes of oral lichenoid lesion caused by an identifiable etiology, such as a hypersensitivity reaction to mechanical irritation or drugs; any other potentially malignant disorders: leukoplakia, erythrolakia, and discoid lupus erythematosus; and a bullous autoimmune disease: pemphigoid and pemphigus.

(2) Any patient without an initial histopathologic diagnosis of OLP and development of OSCC during a follow-up period by biopsy or surgery.

(3) Any patient with diagnosis of OLP concomitant OSCC at the first visit.

(4) Any patient who had not been followed for a total length of time of less than 6 months after being diagnosed with OLP.

The results of 956 patients with clinically diagnosed OLP were initially reviewed; however, 157 patients were excluded because they did not meet the WHO histopathologic diagnostic criteria for OLP, and 281 patients were excluded because of having a follow-up period of less than 6 months after being diagnosed with OLP. Thus, 518 patients with histologically confirmed OLP were selected to be retrospectively reviewed in this study. The confirmation histopathologic diagnosis was performed by 2 oral pathologists (Dr. Jiang Li and Dr. Li-Zhen Wang, Shanghai Jiao Tong University School of Medicine) from hematoxylin-eosin–stained slides. The archived files and pathology reports were reviewed to confirm that OSCC occurred in the same site that was previously diagnosed as OLP.

As described in previous studies,4,8 the clinical forms of OLP were classified in this study as “white lichen” for patients presenting with reticular, popular, or plaquelike OLP lesions, and as “red lichen” for patients presenting with atrophic, erosive, or bullous lesions, independently of whether or not these coincided with white lichen lesions at the periphery, or in other sites. Information regarding age, gender, and the clinical form of OLP at the time of initial diagnosis were all documented. History of cigarette smoking, alcohol use, systemic disease, family history (i.e., in first-degree relatives) of OLP or oral cancer, and use of drugs by these patients were also reviewed and analyzed. Specific drugs considered in this review (which have been associated with causing oral lichenoid lesions) included heavy metal agents (e.g., lithium, gold), antihypertensive drugs, hypoglycemic drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and antimicrobial drugs. Patients reporting the use of any of these drugs were excluded from this study. This study was approved by the institutional review board of Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine.

RESULTS

The follow-up period of the 518 patients with OLP after initial diagnosis ranged from 6 months to 21.5 years, with a mean (SD) of 40 (37) months. There were 193 (37.3%) patients classified as “long duration” (time elapsed since initial diagnosis of OLP ≥ 40 months) with a mean duration of 78 months, and 325 (62.7%) classified as “short duration” (time elapsed since initial diagnosis of OLP <40 months) with a mean duration of 18 months. There were 353 females and 165 males (ratio female:male = 2.1:1.0) with the mean (SD) age at diagnosis of 46.3 (12.0) years ranging from 9 to 81 years. At initial presentation, white lichen was seen in 271 (52.3%) patients, and red lichen was observed in 247 (47.7%) patients. Of these, history of cigarette smoking and alcohol use were recorded in 43 (8.3%) and 41 (7.9%) cases, respectively. The incidence of systemic diseases included hypertension (10.0%), hepatitis B (6.9%), arthritis (1.7%), and diabetes mellitus (1.4%). Family history of OLP or oral cancer was documented in 6 (1.2%) and 2 (0.4%) patients, respectively.
Of the 518 patients diagnosed with OLP, 5 patients (0.96%) developed OSCC in sites that were previously diagnosed as OLP. Early-stage (I or II) OSCC was detected in each of the 5 patients. The mean interval of time between the initial diagnosis of OLP and the diagnosis of OSCC (i.e., “latency”) in these 5 patients was 70.4 months. Unfortunately, 1 patient, designated as case 2 (Table I), died of metastatic disease 46 months after the initial diagnosis of OSCC. All of the patients who developed OSCC were females, with a mean age at the initial diagnosis of OLP of 50.6 years. Both white (n = 1) or red (n = 4) lichen were reported as the initial clinical form of OLP. None of these patients had a history of smoking or alcohol use. Four of the patients who developed OSCC had a history of prior treatment with both topical and systemic corticosteroids. The duration of treatment with systemic corticosteroids in these patients ranged from 1 to 13 months (Table I).

**DISCUSSION**

The present study attempts to determine the occurrence and characteristics of OSCC developing in lesions that were previously diagnosed as OLP in a relatively large cohort from eastern China. Two critical variables were evaluated with regard to the malignant transformation of OLP: the initial diagnosis of OLP and the latency from the initial diagnosis to development of OSCC. In this context, patients in our series were diagnosed with OLP according to WHO clinical and histopathologic criteria. Moreover, we excluded any patient with diagnosis of OLP and concomitant OSCC at the first visit, as well as those with a follow-up period of less than 6 months after initially being diagnosed with OLP. A short time interval between diagnosis of OLP and OSCC could lead to overestimation of the true occurrence of OLP transformation and potentially suggest these 2 diseases were synchronous, in accordance with the criteria of Gandolfo et al. and Bermejo-Fenoll et al. A frequency (0.96%) of patients with OLP developed OSCC in this study, which is consistent with that reported in other series. The mean latency for the development of OSCC in sites previously diagnosed as OLP was 70.4 months, with a range of 20 to 130 months, as compared with a mean of time of follow-up observation of 40 months in our cohort.

We observed the red form of OLP was more frequent than the white form in patients who developed OSCC. In the reported series, some authors found that the atrophic-erosive form of OLP predisposed to oral cancer development, whereas others believed that malignant transformation may occur in all clinical forms of OLP, and atrophic-erosive form had no significantly higher risk of transformation. It seems the malignant transformation of OLP is a complex process influenced by various factors, including clinical form, duration of disease, treatment history, and host immunity.

### Table I. Characteristics of OLP patients who developed oral cancer

| Case | Age (y) | Gender | OLP clinical form | Site of OLP biopsy | Size of OLP biopsy | Latency* (M) | Status of tumor | Tumor stage | Site of tumor | Smoking or alcohol use | Family history† | Prior corticosteroid therapy | Systemic disease |
|------|---------|--------|-------------------|--------------------|-------------------|-------------|----------------|-------------|--------------|------------------------|----------------|---------------------------|-----------------|---|
| 1    | 50      | Female | Red               | Lower lip          | 121               | SCC         | Early          | Early Lower lip | No           | No                     | Yes            | Yes                       | No              |
| 2    | 46      | Female | Red               | Left BM            | 130               | SCC         | Early          | Left BM       | No           | No                     | Yes            | Yes                       | No              |
| 3    | 58      | Female | Red               | Left BM            | 51                | SCC         | Early          | Left lower gingiva | No           | No                     | Yes            | Yes                       | No              |
| 4    | 48      | Female | White             | Ventral tongue     | 20                | SCC         | Early          | Left lower gingiva | No           | No                     | Yes            | Yes                       | No              |
| 5    | 51      | Female | Red               | Gingiva, BM        | 20                | SCC         | Early          | Left lower gingiva | No           | No                     | Yes            | Yes                       | No              |

BM, buccal mucosa; OLP, oral lichen planus; SCC, squamous cell carcinoma. M, months. The interval of time (in months) between the initial diagnosis of OLP and the diagnosis of SCC. The presence of a family history (i.e., in first-degree relatives) of OLP or oral cancer.
change was independent of the clinical type of OLP. To date, there is no sufficient explanation of the mechanism of malignant transformation.

Although oral cancer occurs more commonly in males in China, a greater predilection for the development of OSCC in females diagnosed with OLP has been previously reported by most studies. In our study, all of the patients with OLP who later developed OSCC were females, as consistent with existing literature. This may be partly attributed to the fact that women significantly outnumbered men (2.1:1.0) both in our study cohort, and also in the population of patients seen in our clinic in general. Furthermore, very few women have the habit of smoking and alcohol intake in the geographic region and population of patients served by our clinic. In our study, smoking and alcohol use were not reported or observed in the 5 patients with OLP who developed OSCC. Also, no relationship between smoking and/or alcohol use in patients with OLP who developed OSCC has been reported in the published literature. Only a few patients enrolled in this study reported a positive family history of OLP or oral cancer, and none of the patients who developed OSCC reported a positive family history of oral cancer. This does not provide definitive insight into a genetic basis as to whether OLP and development of OSCC has a strong genetic etiopathogenesis, and this was not assessed by this study.

Of further interest is the possible influence of immunosuppressive therapy on the patients with OPL who developed OSCC. Topical and systemic corticosteroids are the most widely used treatment of OLP. This therapy is recommended as the most effective medication to heal erosive and atrophic lesions and relieve symptoms; however, there remains some concern that this therapy might theoretically impair immune defenses, which may also increase the chances of developing OSCC. Herein, prior corticosteroid therapy in the 4 patients who developed OSCC was documented. We highlighted 1 patient (case 2, Table I) who received prior systemic corticosteroids 13 months before OSCC diagnosis, and died of metastatic disease 46 months after cancer diagnosis. In our opinion, treatment with corticosteroids may have increased the chance of developing OSCC in 4 of these patients owing to the immunosuppressive effect of these drugs. However, the presence or degree of any specific immunosuppressive effect of corticosteroids in these patients was not established by this study. Together, few significant potential contributing factors were identified that might be associated with an increased risk for the development of OSCC in the present group of patients with OLP. However, gender-specific factors, such as hormone replacement therapy or human papilloma virus infection, maybe correlate with an increased risk. Further studies are needed to investigate the roles of these factors in the development of OSCC in patients with OLP.

In summary, the incidence of OSCC developing in lesions previously diagnosed as OLP is less than 1% and females were more commonly affected. These cases appear to represent the transformation of OLP into OSCC; however, it cannot be entirely ruled out that these cases represent de novo OSCC, as it is possible that potential factors not directly related to OLP may play a role in the malignant process and may occur in the mouths of patients who also happened to have OLP. Also, there are too few cases to comment on whether corticosteroid/immunosuppressive therapy plays a role in the development of OSCC in patients with OLP.

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