The issue as to whether oral lichen planus is a premalignant disorder is still controversial. This study aimed to examine oral malignancies associated with oral lichen planus and to investigate whether oral lichen planus has an intrinsic malignant potential or whether there are also contributing external risk factors. A retrospective cohort study in 200 Caucasian patients with oral lichen planus was conducted between 1991 and 2003. Aspects such as sex, age, clinical variant, affected anatomical sites, duration of the disease, histopathology, prior immunosuppressive treatment, exposure to potential carcinogens and other concomitant diseases were examined. Histopathological examination was repeated during the follow-up if a malignancy was suspected. Three (1.5%) of the 200 patients developed an oral squamous cell carcinoma at the same site following the initial diagnosis of oral lichen planus after a period of 3–6 years (mean 4.3 years). Contributing external risk factors were also noted in two of the three patients (smoking for 20 years and systemic immunosuppressive treatment for 2 years). The exact incidence of malignant transformation is difficult to establish, because of the low number of patients and because of the possible contribution of external risk factors, which may be relevant in oral malignancy. Key words: oral lichen planus; premalignancy; oral squamous cell carcinoma.

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Oral lichen planus (OLP) has a prevalence of about 0.5–2% in the general population. It is a disease affecting the middle-aged and the elderly and the female-to-male ratio is about 2:1. The diagnosis of OLP is based on a combination of characteristic clinical findings, history and histopathology (1–3). Oral lichen planus can be categorized into several clinical variants. These are usually an asymptomatic, hyperkeratotic (white) variant: reticular with Wickham’s striae, papular or plaque-like. The atrophic or erythematous (red) variant and the erosive or ulcerative (yellow) variants usually have persistent symptoms of pain or stinging and very often minor signs of the hyperkeratotic variant in the surrounding mucosa are also observed (1, 2). It is generally a disease that persists for many years despite several modes of treatment (3).

In Europe, the incidence of malignancies of the oral mucosa is about 4 per 100 000 individuals (0.004%) per year, which represents approximately 1–2% of the total number of malignancies. More men than women are affected (ratio 2 to 3:1). An oral squamous cell carcinoma (OSCC) is encountered in about 80% of the cases (4–6). The clinical presentation of an OSCC may vary from indurated, non-healing ulcers to exophytic, hyperkeratotic masses and less frequently as red, submucosal and slightly indurated lesions with an apparently intact epithelium (5, 7, 8). A verrucous carcinoma is a specific variant of OSCC (9). Histopathological examination generally shows a well-differentiated OSCC. The essential features of OSCC are invasion through the basement membrane and epithelial dysplasia (7, 10). Red areas, rather than white areas, should preferably be biopsied because of the more frequent dysplastic features (8).

Tobacco exposure, alcohol abuse (and especially the combination of the two), poor nutrition, leucoplaikia and erythroplakia are known to be contributing external risk factors in OSCC (5, 11). The predilection sites are the lower lip, the lateral parts of the tongue and the floor of the mouth. The risk of metastasis is largely related to the size of the primary tumour. The average 5-year survival rate is about 50%, in spite of surgery and radiotherapy. Early detection of this malignancy favours the prognosis significantly (5, 6, 8). The possible malignant transformation of OLP still remains a controversial issue in the literature (2, 9, 12–16). The incidence of malignant transformation of OLP into an OSCC is reported to range from 0 to 10% (7). The possible premalignant nature of OLP is very important for the advice that should be recommended to the patient, the recognition of possible risk factors, the necessity for meticulous clinical and histopathological examination, adequate treatment and the schedule of follow-up.

The aim of this retrospective study was to determine the incidence of oral malignancies associated with OLP.
and to investigate whether OLP is intrinsically premalignant or whether there are also contributing external risk factors.

PATIENTS AND METHODS

We conducted a retrospective cohort study in 200 Caucasian patients with a confirmed diagnosis of OLP based on the medical history and physical and histopathological examination. Special attention was paid to aspects such as clinical variant of OLP, involved anatomical site, duration of OLP, sex, race, age, histopathology, prior treatment (topical and/or systemic immunosuppressive medication), exposure to tobacco, alcohol abuse, candidosis, concomitant extra-oral lichen planus and associated systemic diseases.

This study was conducted from 1991 to 1993 at the Department of Dermatology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands and continued from 1994 to 2003 at the Department of Dermatology, Albert Schweitzer Hospital, Dordrecht, the Netherlands.

Exclusion criteria were an age younger than 18 years, a first history of any kind of oral malignancy, a history of two or more oral malignancies, and death from any cause before the follow-up period.

All patients were followed up at least once a year and more often if necessary depending on the symptomatology, the extent and the severity of OLP and the possible accompanying external risk factors. The patients were requested to consult us earlier than the regular visit if the oral lesions progressed. A total of 200 Caucasian patients, 132 women and 68 men, aged 25–83 years (mean age 53 years), were evaluated in this study. The hyperkeratotic variant of OLP was predominantly seen in 92 (46%) patients (61 women and 31 men), the erosive or ulcerative variant in 67 (33.5%) patients (41 women and 26 men) and the atrophic or erythematous variant in 41 (20.5%) patients (30 women and 11 men). The sites affected by OLP were, in diminishing frequency, the buccal mucosa (symmetrical), the lateral margins of the tongue, the gingiva, the labial mucosa and the dorsal part of the tongue. Lesions on the palate and the floor of the mouth were observed in only five patients.

Histopathological examination showed ‘evident OLP’ in 89 patients, ‘compatible with OLP’ in 88 patients and ‘non-specific changes’ in 23 patients, without a significant difference between men and women. Based on clinical and histopathological examination, 38 (19%) patients also had cutaneous lichen planus and 12 (9%) women with OLP had symptomatic vulvar and vaginal lichenoid lesions.

The follow-up period ranged from 7 to 13 years (mean 10 years) and an OSCC was encountered at the same site of OLP in 3 of the 200 patients with OLP after a mean period of 4.3 years. The characteristics of these three patients are shown in Table I. Histopathological examination was repeated in four other patients during the follow-up period, because a malignancy was suspected. However, none of these four patients had an OSCC. There was no change in the symptoms of OLP in the three patients at the time when an OSCC was detected. All the three patients were effectively treated for OSCC. The male patient had smoked approximately 25 cigarettes a day for 20 years and stopped smoking 0.5 years after the diagnosis of OLP. The exact treatment regime is beyond the scope of this study. In the follow-up period of 3–5 years (mean 4 years) no tumour recurrences or metastases were observed.

Statistical analysis was based on the incidence of 4 oral malignancies per 100 000 individuals per year in Europe versus 1, 2 or 3 cases of OSCC of 2000 person-years in our study.
The probability of at least one case of OSCC in our cohort study is $p = 0.08$ according to the Poisson distribution, which could be attributed to chance alone. However, the probability of at least two or three cases is $p = 0.003$ and $p = 0.00008$, respectively, which is statistically significant. This means that it is highly improbable that at least two or three cases of OSCC in our study were encountered by chance alone.

**DISCUSSION**

Hallopeau already reported a case of OLP with malignant degeneration in 1910 (17). Krutchkoff et al. criticized the literature on the malignant transformation of OLP from the period 1950–1976 and accepted only 15 (7%) of the 223 published cases as adequately documented (18). As shown in Table II, Van der Meij et al. used the same criteria from the period 1977–1999 and accepted 33 (34%) of the 98 reported cases as adequately documented (13). Their objections were largely based on the uncertainty of the initial diagnosis of OLP on clinical and histopathological grounds, the occurrence of oral cancers remote from the anatomic site of OLP and the frequently inadequate information on prior exposure to potentially carcinogenic substances (13, 19). Several remarks can be made as regards these objections.

Even if a reliable biopsy is obtained from the patient at the first visit to confirm the initial diagnosis of OLP, there is a significant inter- and intra-observer variation in the interpretation of the criteria for establishing the diagnosis of OLP despite the criteria by the World Health Organization (9, 19). Moreover, important aspects such as dysplastic or atypical changes are not always clearly and carefully detailed in the histopathological reports. Therefore, the results reported in different studies are not always easy to compare.
OSCC occurs at a site remote from OLP, the direct relationship between the two may be disputed, because an OSCC may obviously occur in the absence of OLP (13, 18). Exposure to potentially carcinogenic substances could have occurred several years earlier, so that it could be easily missed as a relevant contributing external risk factor because OLP persists for many years. It is difficult to establish whether there is a synergistic premalignant effect in case of exposure to potentially carcinogenic substances (contributing external risk factors) and persistence of OLP (intrinsic risk factor). Moreover, the mucosa is more vulnerable, particularly in the erosive and atrophic variants of OLP (3, 12). The treatment of symptomatic OLP often consists of topical or systemic immunosuppressive medication, which in our opinion may also increase the chances of developing an OSCC. The influence of immunosuppressive medication in a specific case is difficult to establish because the number of malignancies is relatively low. The prevalence of oral cancer varies widely in different parts of the world. Its prevalence is high in parts of south-east Asia, especially in India, where the high prevalence is most likely related to tobacco exposure, betel nut chewing or ‘reverse’ smoking (8). It is reasonable to assume that the prevalence of OLP also varies significantly in various parts of the world; therefore, the prevalence of malignant transformation would also vary (9). A comparison between studies from different geographical areas of the world may thus be very problematic.

Nevertheless, there are other important contributing external risk factors for oral malignancy such as alcohol abuse, exposure to tobacco, candidosis and poor nutrition. These can be identified rather easily and are easy to influence (3, 20). It has been suggested that human papilloma virus and herpes simplex virus are also implicated as risk factors in oral carcinogenesis (3). Aggravating factors such as stress, specific foods (citrus and spicy ingredients), mechanical traumata, irritation or allergy related to dental restorations and poor oral hygiene are also important in OLP (2, 3).

If the criteria used by Krutchkoff et al. (Table II) are applied in our study, then patient B who smoked heavily should be considered as a drop-out (13, 18). In that case, 2 of the 200 patients investigated patients in this study developed an OSCC. Patient A had also received systemic immunosuppressive medication (corticosteroids and cyclosporine) over a period of about 2 years, which could have increased the chance of developing a malignancy. In that case, only 1 of the 200 patients may be regarded as a real intrinsic malignancy. Therefore, it still remains unclear whether OLP has an intrinsic malignant potential because a single OSCC may occur by chance alone. In that case, OLP does not fulfill the WHO criterion for a precancerous condition: ‘a generalized state associated with a significant increased risk of cancer’ (3, 21, 22).

In our opinion, it is very likely that there is a synergy between intrinsic (chronic inflammatory features in OLP) and contributing external risk factors in possible malignant transformation in OLP. It has been reported that a specific clinical variant of OLP (either hyperkeratosic or erosive) had a higher chance of transformation into an OSCC (3, 12). The results of other studies including our study fail to support this because of the low number of patients. The follow-up period also varied from one to four visits per year in other studies (21, 22). A more frequent follow-up visit does not necessarily lead to an improved prognosis for OLP patients with an OSCC (23). We recommend a follow-up of at least one or two visits per year as long as OLP persists. A careful physical examination at each visit is imperative and histopathological examination should be repeated if a malignancy is suspected. From a practical point of view, we concur with Voute et al. in that we are also somewhat reluctant to routinely inform each patient with OLP of the possible premalignant character of their lesions, particularly if contributing external risk factors are also involved (21).

The results of this study showed that it is mandatory to establish a correct diagnosis of OLP based on history, clinical examination and histopathology. Nonetheless, the results failed to provide an answer to the controversial issue of whether oral lichen planus has an intrinsic malignant potential. The exact incidence of OSCC in patients with OLP is difficult to establish because of the low number of patients involved and because other contributing external risk factors may also be relevant for developing a malignancy. Further larger cohort studies are necessary to resolve this issue.

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