Objective: The aim of this review was to analyse, systematically, hospital-based epidemiological information concerning the malignant transformation rate (MTR) of oral leukoplakia (OL) in a Chinese population, as well as the associated risk factors. Methods: Four electronic databases were searched for studies dealing with OL and related risk factors, including age, gender, type of lesion, site, and smoking and drinking habits. Results: The MTR of OL in the hospital-based Chinese population ranged from 4% to 13%, based on the studies analysed. Regarding risk factors, we found that female patients had a higher MTR than male patients, and that patients older than 50 years of age also had a higher MTR. Patients who smoked had a lower MTR, while alcohol consumption seemed to have no association with MTR. Malignant transformation occurred most commonly on the tongue. Regarding lesion type, non-homogeneous OL had a higher MTR, with the granular type having the highest MTR. Our results regarding the epidemiology of OL showed a similar trend to those reported in western populations and provided preliminary epidemiological information on the Chinese population. Conclusions: Our findings show that female gender, age >50 years and non-homogeneous OL are risk factors for malignant transformation. It is important to develop clinical strategies to educate, diagnose and treat patients with OL and to minimise the MTR of OL.

Key words: Oral leukoplakia, malignant transformation, risk factor, Chinese population

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is recognised widely as the most common type of head and neck cancer, with a 5-year survival rate of only ~50% despite the development of various treatments in the past three decades.

Reports have indicated that 15.8–48.0% of patients with OSCC have had a history of oral leukoplakia (OL) when diagnosed. Identifying the risk factors for OSCC might help to prevent transformation by initiating adequate and timely intervention.

OL is a prevalent lesion of the oral cavity with the potential for premalignant transformation. In 1978 the World Health Organization (WHO) defined leukoplakia as ‘a white patch on the oral mucosa that can neither be scraped off nor classified as any other diagnosable disease’. However, the definition of leukoplakia was modified in 1987, and in 2005 OL was redefined by the WHO as a potentially malignant disorder. It was defined as ‘a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer’.

Various studies have shown that the rate of malignant transformation of OL varies widely (0.6–20%), probably because of the lack of global standardisation. Epidemiological information on the malignant transformation rate (MTR) of OL in the Chinese population is limited. The first documented study of OL in the Chinese language was published in 1964. Moreover, the MTR was reported to range from 4% to 13% in different surveys conducted in China. Furthermore, risk factors associated with the MTR of OL have not been fully documented. Therefore, there is an urgent need for comprehensive information on the malignant transformation of OL and its associated risk factors in a Chinese population.
Some common risk factors associated with the MTR of OL are female gender, age >50 years, non-homogeneous OL, widespread lesions with multiple foci and tongue and floor-of-mouth lesions. In addition, the MTR of OL varies with lifestyle-related habits, such as tobacco and alcohol use. Although commonly overlooked, viral infection, the size of the lesion and conservative treatment might also be risk factors. Some of these risk factors are associated with ethnic/cultural and environmental factors. For example, in China, there are a larger number of smokers compared with other countries, and eating habits and other environmental factors are also different. Therefore, the aim of this review was to analyse systematically the epidemiological characteristics and supply basic information on the MTR of OL in a Chinese population. Early identification of lesions at risk would permit early intervention, which might improve the outcome.

MATERIALS AND METHODS

Study selection, data extraction and study quality assessment

Four online databases – the China National Knowledge Infrastructure (CNKI), WANFANG DATA, the Chinese BioMedical Literature Database (CBM) and PubMed – were searched by two independent investigators and complemented by hand searching. Articles were searched for use of the following key words in Chinese and English: ‘oral leukoplakia’ or ‘oral pre-cancerous lesion’ or ‘oral cancer’ and ‘malignant transformation’ and ‘China or Chinese’. The epidemiological information was searched using ‘epidemiological study’ or ‘epidemiology or descriptive’ as search terms. The study type included ‘cohort’, ‘retrospective’ or ‘cross-sectional’ study. The risk factors for malignant transformation of OL included age, gender, type of lesion, site, and smoking and drinking habits. The affected sites observed in this paper were limited to the oral cavity, and included: C00, the lip; C01, the base of the tongue; C02, the oral tongue; C03, the gums; C04, the floor of the mouth; C05, the palate but not the tonsil; and C06, other unspecified parts of the mouth.

The data were obtained from journals published from 1992 until April 2015 in both Chinese and English. Patients diagnosed with OL based on a combination of definite clinical and pathological manifestations were recruited for the present review.

Data extraction and analysis were performed independently by two reviewers (G.Y.S. and L.S.). The extracted data included authors, city of origin, year of publication, type of study, total number of patients with OL, patients’ gender and age, drinking habits of patients with OL, smoking habits of patients with OL, lesion sites, clinical classification of OL lesions, diagnostic criteria and other detailed information for the review. Any disagreement was resolved by discussion or by using a third reviewer (L.M.Y.); thus, there was a low risk of sampling bias and selection bias.

Study quality and bias were assessed using the Cochrane Handbook for Systematic Reviews of Interventions (ver. 5.0.2). The studies included in our review were all retrospective cross-sectional studies conducted by reviewing historical medical records. No intervention was applied on the objects; therefore, they were judged to have a low risk of within-study bias.

Data analysis

Statistical analyses were conducted using Review Manager 5.3 (Cochrane Collaboration) and Microsoft Excel 2013 (15.0.4797.1000). Subgroup analysis was undertaken for subsets of patients (male patients, female patients, drinkers, non-drinkers, smokers and non-smokers) and subsets of OL (clinical classification). The estimate of the MTR was expressed as pooled MTR together with 95% confidence interval (95% CI). An I² test was performed to evaluate the heterogeneity of the studies, ranging from 0% to 100%; I² values of 25% and 50% were used as cutoffs for modest and high heterogeneity. If no significant heterogeneity was found, a fixed-effect model was used; otherwise, a random-effect model was used.

RESULTS

Characteristics of included studies

Among the 2380 publications initially identified in the databases, studies were excluded because they were duplicates, did not meet the inclusion criteria, the full-text articles could not be obtained or for other reasons. In total, eight studies were included in the systematic review (Table 1), among which six involved gender differences, four involved smoking or non-smoking patients, three involved drinking or non-drinking patients and four involved detailed clinical classification of OL (Table 1).

The reported MTR of OL ranged from 4.45% to 13.62% (Table 1) in the eight surveys included. The heterogeneity among them was high (I² = 94%; P < 0.00001); therefore, a random-effect model was used for the meta-analysis, and the pooled MTR (95% CI) was 9.00 (6.00–13.00)%.

Relationship between the MTR of OL and gender

Six articles reported differences in the MTR between male and female patients. A random-effect model was
chosen for the meta-analysis because of heterogeneity among the studies [male $I^2 = 94\%$ ($P < 0.00001$); female $I^2 = 84\%$ ($P < 0.00001$)]. The results showed that the pooled MTR was higher in female patients (0.14; 95% CI: 0.09–0.19) than in male patients (0.09; 95% CI: 0.04–0.13). The male : female ratio for the MTR of OL was 1:1.56 (Table 2).

### Relationship between the MTR of OL and tobacco smoking

In most studies, the MTR of OL in smokers was lower (Table 3). The exception was a study by Guan et al., in which a higher MTR was reported in smokers than in non-smokers (18.97% vs. 3.85%); moreover, in that study, a direct association was found between the MTR and the number of cigarettes smoked. In the study by Lan et al., no significant difference was found between the two groups.

Among the four surveys, the heterogeneity was high [smokers $I^2 = 56\%$ ($P = 0.08$); non-smokers $I^2 = 78\%$ ($P = 0.003$)]; therefore, a random-effect model was chosen for the meta-analysis. The results showed a higher MTR in non-smokers [pooled MTR (95% CI) = 0.15 (0.09–0.22)] than in smokers [pooled MTR (95% CI) = 0.09 (0.06–0.12)].

### Relationship between the MTR of OL and alcohol consumption

Heterogeneity was low in the drinkers subgroups ($I^2 = 0\%$; $P = 0.67$) and was high in non-drinkers subgroups ($I^2 = 66\%$; $P = 0.03$); therefore, a fixed-effect model and a random-effect model were used, respectively, for the meta-analysis. The results showed that the pooled MTR of drinking patients was 0.13 (95% CI: 0.10–0.15), which was slightly higher than that of non-drinking patients (0.12; 95% CI: 0.10–0.14) (Table 4). However, only one study demonstrated that drinkers had a higher MTR (16.67%; 95% CI: 5.40–27.94%) compared with non-drinkers (10.00%; 95% CI: 3.80–16.20), and two other studies showed no association between alcohol consumption and the MTR of OL.

### Relationship between the MTR of OL and lesion location

The MTR of OL at different sites was determined in six surveys (Table 5). According to the first four surveys, lesions located on the tongue had the highest MTR. Moreover, the MTRs of lesions on the lateral/ventral tongue were much higher than those of lesions on the dorsal tongue. The MTRs of lesions of the buccal mucosa, lip, palate and gingiva were much

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**Table 1** Details of the eight studies included in the systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>City</th>
<th>Total patients with OL</th>
<th>Gender of OL patients</th>
<th>Drinkers in OL patients</th>
<th>Smokers in OL patients</th>
<th>Subtypes of lesions in OL patients Malignant transformation cases [MTR(%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lan et al.</td>
<td>Retrospective analysis</td>
<td>Beijing</td>
<td>409</td>
<td>208</td>
<td>42</td>
<td>201</td>
<td>118</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Prospective analysis</td>
<td>Shanghai</td>
<td>576</td>
<td>350</td>
<td>226</td>
<td>228</td>
<td>107</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>Retrospective analysis</td>
<td>Taiwan</td>
<td>1046</td>
<td>956</td>
<td>90</td>
<td>370</td>
<td>676</td>
</tr>
<tr>
<td>Shi</td>
<td>Prospective analysis</td>
<td>Shanghai</td>
<td>235</td>
<td>152</td>
<td>83</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zhu et al.</td>
<td>Retrospective analysis</td>
<td>Hebei &amp; Shanxi</td>
<td>150</td>
<td>98</td>
<td>52</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gao et al.</td>
<td>Retrospective analysis</td>
<td>Beijing</td>
<td>1832</td>
<td>959</td>
<td>873</td>
<td>595</td>
<td>55</td>
</tr>
<tr>
<td>Guan et al.</td>
<td>Retrospective analysis</td>
<td>Beijing</td>
<td>211</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ge et al.</td>
<td>Retrospective analysis</td>
<td>Beijing</td>
<td>211</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not available. Values are given as n.

MTR, malignant transformation rate; OL, oral leukoplakia.
lower. Lan et al. classified the OL sites into a high-risk zone (including the tongue and the floor of the mouth) and a low-risk zone (including the buccal mucosa, lip, palate and gingiva); their results demonstrated that the MTR rate for lesions in the high-risk zone was higher compared with lesions located in the low-risk zone (20% vs. 10.2%)6.

Relationship between the MTR of OL and age

As shown in Table 6, Wang et al. reported that the MTR of OL was higher in the 41–60 years age group13, while Ge et al. narrowed down the range to 50–59 years3. Lee et al. found that patients older than 50 years of age were at a significantly higher risk of
MTR than were younger patients (odds ratio = 2.03; 95% CI = 1.11–3.72). Wang et al. reported that the MTR of OL in women 31–60 years of age was significantly greater than that in men of the same age group. However, men over 60 years of age had a much higher MTR than did women over 80 years of age.

**Relationship between MTR and the clinical classification of OL**

Table 7 shows the MTR in different subtypes of OL. The heterogeneity of homogeneous, non-homogeneous and speckled, granular subgroups was high or modest (respectively: $I^2 = 66\%$, $P = 0.03$; $I^2 = 77\%$, $P = 0.005$; $I^2 = 66\%$, $P = 0.03$; and $I^2 = 49\%$, $P = 0.12$), while the heterogeneity of the verrucous subgroup was acceptable ($I^2 = 0\%$, $P = 0.42$). Thus, a random-effect model and a fixed-effect model were used, respectively.

The results showed that the MTR of homogeneous-type OL [0.61–7.13\%; pooled MTR (95\% CI) = 0.07 (0.05–0.12)] was lower than that of the non-homogeneous-type [5.88–58.33\%; pooled MTR (95\% CI) = 0.25 (0.19–0.31)]. Among cases of non-homogeneous OL, granular (or nodular) OL had the highest pooled MTR (0.33; 95\% CI: 0.22–0.47) and verrucous OL had the lowest pooled MTR (0.22; 95\% CI: 0.17–0.29).

**DISCUSSION**

In this review, we analysed the data on malignant transformation of OL and presented the hospital-based epidemiological as well as clinical characteristics of these Chinese patients. The analysis in this review showed that women tended to have a higher MTR in China. This finding is similar to that reported in other published studies outside China. There is no clear explanation for this observation; a possible reason might be related to the lower smoking rate among women (also in China) and therefore the OL in a higher number of female patients in China may be idiopathic. Schepman et al. and Silverman et al. also revealed an association between a high MTR of OL and absence of smoking habits only in women. In addition, one study from China also mentioned that younger women might have a higher MTR than older women.

In this analysis, we found that patients who smoke have a lower MTR of OL; however, the reasons for this remain unclear. Many papers on OL have shown that malignant transformation of OL might be related to oral habits; however, the results are controversial. Some studies showed that the potential for carcinogenesis might be lower among smokers (11, 23, 24). Other studies differed in their findings and concluded that heavy smokers had multiple and larger lesions compared with smokers who smoked less frequently.

In China, betel quid (BQ) chewing, a traditional and popular habit, is associated with an increased risk of oral mucosal diseases, including OL. BQ chewing, whether with tobacco or not, is a risk factor for some types of cancer, as observed in many surveys. Shiu found that the relative risk of malignant transformation of OL was 1.04. These findings indicate that while BQ chewing is a risk factor for malignant transformation of OL, it has no significant relationship with the occurrence of OL. A retrospective study showed that BQ chewers might have a higher risk of developing OL (1.0–5.0\% for OL; 0.02–0.05\% for oral cancer). The study showed that the relative risk of OL transformation associated with BQ chewing was only 0.40 (10.08\% in BQ chewers (80/794 cases); 21.83\% in non-BQ chewers (55/252 cases)) implying a negative association between BQ chewing and OL transformation.

In most studies there was no significant difference between drinkers and non-drinkers in the MTR of OL; for example, a large-scale study of 320 patients in Shanghai showed a MTR of OL of 16.33\% (12/72) in drinkers versus 14.29\% (12/84) in non-drinkers. Even though alcohol alone was not found to be associated with the onset of leukoplakia, it was found to have some synergistic effect with tobacco on the development of both leukoplakia and oral cancer. For example, a case–control study in the UK showed that alcohol was linked to smoking as one of the risk factors for dysplasia.
Regarding risk site, we found that the tongue was the most common site of malignant transformation. Several studies showed that most carcinomas which develop from leukoplakia are found on the lateral borders of the tongue or on the floor of the mouth, which are referred to as high-risk sites\textsuperscript{31,32}. The buccal mucosa, which was commonly recognised as the most frequent site of OL\textsuperscript{33}, had a much lower MTR\textsuperscript{31,34}. However, Lee \textit{et al.} found that, in men, most (65.7\%) lesions with malignant transformation were located in the buccal mucosa; this is probably related to the high prevalence of BQ chewing in male patients. In addition, other studies found that sites in the oral cavity were associated predominantly with malignant transformation\textsuperscript{23,35}. Such a discrepancy might be the result of differences in oral habits and other local risk factors\textsuperscript{12}.

In our review, we found that the malignant transformation of OL occurred more often in patients $>$ 50 years of age, which is in accordance with the results of other studies published worldwide\textsuperscript{34,36}. Lan \textit{et al.} analysed the relationship between age and pathological staging of OL, and found that patients with severe dysplasia or squamous cell carcinoma were significantly older ($P < 0.01$) than patients with moderate dysplasia ($P = 0.000$) and with simple hyperplasia ($P = 0.013$)\textsuperscript{2}. The higher MTR in older patients might suggest that the longer the exposure to OL, the higher the occurrence of malignant transformation\textsuperscript{12,23}.

Our results also showed that non-homogeneous OL had a higher risk of malignant transformation. Specifically, the granular type had the highest risk. Several other researchers reported that the MTR of the speckled type or non-homogeneous leukoplakia was higher than that of homogeneous leukoplakia\textsuperscript{37,38}. A 5-year survey on 53 cases of verrucous OL showed that 42\% of the patients underwent carcinogenesis and seven patients were in the process of developing a different degree of dysplasia\textsuperscript{39}.

Generally, a higher severity of dysplasia correlates with a higher MTR. A study including 1832 patients from Peking University School of Stomatology showed that the MTR was consistent with the degree of dysplasia: the MTR was significantly higher in severe dysplasia than in simple hyperplasia\textsuperscript{17}. However, other authors found no relationship between epithelial dysplasia and malignant transformation\textsuperscript{40}, probably because in cases of leukoplakia with moderate or severe dysplasia, the lesion was often immediately excised after biopsy\textsuperscript{12}.

This review is the first to analyse systematically the hospital-based epidemiological and clinical characteristics of the MTR of OL in the Chinese population. We found that female gender, older age, absence of smoking habits, localisation of lesions on the tongue and

### Table 7. Malignant transformation rate (MTR) according to the clinical classification of oral leukoplakia (OL)

<table>
<thead>
<tr>
<th>Study</th>
<th>Individuals</th>
<th>Homogeneous</th>
<th>Non-homogeneous</th>
<th>Veruous</th>
<th>Pooled MTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lan \textit{et al.}\textsuperscript{36}</td>
<td>6 302</td>
<td>0.07 (0.05–0.12)</td>
<td>0.49 (0.26–0.57)</td>
<td>0.18 (0.09–0.34)</td>
<td>0.27 (0.19–0.36)</td>
</tr>
<tr>
<td>Lee \textit{et al.}\textsuperscript{34}</td>
<td>14 421</td>
<td>0.07 (0.05–0.10)</td>
<td>0.41 (0.15–0.22)</td>
<td>0.24 (0.17–0.32)</td>
<td>0.21 (0.18–0.24)</td>
</tr>
<tr>
<td>Shi\textsuperscript{15}</td>
<td>193</td>
<td>0.12 (0.07–0.17)</td>
<td>0.37 (0.19–0.60)</td>
<td>0.06 (0.01–0.32)</td>
<td>0.24 (0.11–0.37)</td>
</tr>
<tr>
<td>Zhu \textit{et al.}\textsuperscript{37}</td>
<td>16 117</td>
<td>0.01 (0.00–0.06)</td>
<td>0.30 (0.10–0.62)</td>
<td>0.38 (0.31–0.48)</td>
<td>0.28 (0.09–0.59)</td>
</tr>
<tr>
<td>Total</td>
<td>1033</td>
<td>0.07 (0.05–0.12)</td>
<td>0.30 (0.11–0.46)</td>
<td>0.33 (0.22–0.47)</td>
<td>0.25 (0.19–0.31)</td>
</tr>
</tbody>
</table>

Values are given as $n$ or mean ± 95% confidence interval.
non-homogeneous lesion type were associated with a higher MTR in the Chinese population. Our results provided basic information of the MTR of OL in a hospital-based Chinese population and this might help reduce the number of patients experiencing malignant transformation by initiating adequate interventions.

One of the limitations of our review is that not all the risk factors for malignant transformation of OL were included. For example, infection with a high-risk genotype of human papillomavirus (HPV) is a well-known independent risk factor for oral cancer; however, no information about HPV infection and the MTR of OL were found in the selected studies. Another limitation is the representativeness of the studies included in this review, which may not truly reflect the situation throughout China. The published studies that were used in this review were conducted in large cities such as Beijing or Shanghai, and did not include any rural areas. The environmental and living conditions in different regions might be reflected in the MTR of OL. Therefore, considering the large population in China, studies in different regions are required to provide better representation of the overall Chinese population.

CONCLUSIONS

In this review, we found that the reported MTR of OL in the hospital-based Chinese population ranged from 4% to 13%. Female patients and patients > 50 years of age have a higher MTR. Furthermore, patients who smoke have a lower MTR of OL, and drinking habits had no influence. The tongue was the most common location of malignant transformation of OL. Finally, non-homogeneous OL had a higher risk of malignant transformation. This study supplied basic information concerning the MTR of OL in the Chinese population. These data will help dental practitioners in China identify at-risk patients, allowing them to reduce the malignant transformation of OL by prompt intervention.

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Conflict of interest

The authors declare that they have no competing interests.

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Oral leukoplakia in a Chinese population

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