

Hospital-based epidemiological and clinical characterisation of the malignant transformation of oral leukoplakia in a Chinese population

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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^{1,2}.

Reports have indicated that 15.8–48.0% of patients with OSCC have had a history of oral leukoplakia (OL) when diagnosed^{3–6}. 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 1987⁷, 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’^{8–10}.

Various studies have shown that the rate of malignant transformation of OL varies widely (0.6–20%), probably because of the lack of global standardisation¹. 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 1964¹. Moreover, the MTR was reported to range from 4% to 13% in different surveys conducted in China^{2–4}. 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 OL⁵, widespread lesions with multiple foci⁶ and tongue and floor-of-mouth lesions²⁻⁵. In addition, the MTR of OL varies with lifestyle-related habits, such as tobacco and alcohol use¹¹. Although commonly overlooked, viral infection, the size of the lesion and conservative treatment might also be risk factors^{6,12}. 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 countries¹³, 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 precancerous 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 I^2 test was performed to evaluate the heterogeneity of the studies, ranging from 0% to 100%; I^2 values of 25% and 50% were used as cut-offs for modest and high heterogeneity. If no significant heterogeneity was found, a fixed-effect model was used to calculate the pooled MTR; 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 ($I^2 = 94\%$; $P < 0.00001$); 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

Table 1 Details of the eight studies included in the systemic review

Study	Study type	City	Total patients with OL	Gender of OL patients		Drinkers in OL patients		Smokers in OL patients		Subtypes of lesions in OL patients				Malignant transformation cases [MTR(%)]
				Male	Female	Drinkers	Non-drinkers	Smokers	Non-smokers	Homogeneous	Speckled	Granular	Verrucous	
Lan et al. ²	Retrospective analysis	Beijing	409	208	201	42	90	118	107	302	37	32	38	52 (12.7)
Wang et al. ¹³	Prospective analysis	Shanghai	576	350	226	92	397	228	270	NA	NA	NA	NA	66 (11.5)
Lee et al. ¹⁴	Retrospective analysis	Taiwan	1046	956	90	370	676	845	201	421	430	78	113	135 (12.9)
Shi ¹⁵	Prospective analysis	Shanghai	235	152	83	NA	NA	NA	NA	193	19	6	17	32 (13.62)
Zhu et al. ¹⁶	Retrospective analysis	Hebei & Shanxi	150	98	52	NA	NA	NA	NA	117	10	12	11	14 (9.33)
Gao et al. ¹⁷	Retrospective analysis	Beijing	1832	959	873	NA	NA	NA	NA	NA	NA	NA	NA	85 (4.64)
Guan et al. ⁴	Retrospective analysis	Beijing	110	NA	NA	NA	NA	58	52	NA	NA	NA	NA	13 (11.82)
Ge et al. ³	Retrospective analysis	Beijing	211	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14 (6.64)

NA, not available.
 Values are given as n.
 MTR malignant transformation rate, OL oral leukoplakia.

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 smoked¹⁴. In the study by Lan et al., no significant difference was found between the two groups².

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^{13,15–17}, 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

Table 2 Malignant transformation rate (MTR) of oral leukoplakia (OL) according to gender

Study	Study type	City	Individuals		Pooled MTR	
			Male	Female	Male	Female
Shi ¹⁵	Prospective analysis	Shanghai	152	83	0.12 (0.07–0.17)	0.17 (0.09–0.25)
Wang <i>et al.</i> ¹³	Prospective analysis	Shanghai	350	226	0.09 (0.06–0.12)	0.15 (0.10–0.19)
Zhu <i>et al.</i> ¹⁶	Retrospective analysis	Hebei & Shanxi	98	52	0.07 (0.02–0.12)	0.13 (0.04–0.23)
Lan <i>et al.</i> ²	Retrospective analysis	Beijing	208	201	0.09 (0.05–0.13)	0.16 (0.11–0.22)
Lee <i>et al.</i> ¹⁴	Retrospective analysis	Taiwan	956	90	0.12 (0.10–0.14)	0.20 (0.12–0.28)
Gao <i>et al.</i> ¹⁷	Retrospective analysis	Beijing	959	873	0.03 (0.02–0.04)	0.07 (0.05–0.08)
Total	NA	NA	2723	1525	0.09 (0.04–0.13)	0.14 (0.09–0.19)

Values are given as *n* or mean ± 95% confidence interval. NA, not available.

Table 3 Malignant transformation rate (MTR) of oral leukoplakia (OL) according to smoking habit

Study	Study type	City	Individuals		Pooled MTR	
			Smokers	Non-smokers	Smokers	Non-smokers
Guan <i>et al.</i> ⁴	Retrospective analysis	Beijing	58	52	0.19 (0.09–0.29)	0.04 (0.01–0.14)
Lan <i>et al.</i> ²	Retrospective analysis	Beijing	118	107	0.08 (0.03–0.12)	0.12 (0.07–0.20)
Lee <i>et al.</i> ¹⁴	Retrospective analysis	Taiwan	845	201	0.10 (0.08–0.12)	0.24 (0.18–0.30)
Wang <i>et al.</i> ¹³	Prospective analysis	Shanghai	228	270	0.07 (0.04–0.10)	0.15 (0.12–0.19)
Total	NA	NA	1249	630	0.09 (0.06–0.12)	0.15 (0.09–0.22)

Values are given as *n* or mean ± 95% confidence interval. NA, not available.

Table 4 Malignant transformation rate (MTR) of oral leukoplakia (OL) according to drinking habit

Study	Study type	City	Individuals		Pooled MTR	
			Drinkers	Non-drinkers	Drinkers	Non-drinkers
Lan <i>et al.</i> ²	Retrospective analysis	Beijing	42	90	0.17 (0.05–0.28)	0.10 (0.04–0.16)
Lee <i>et al.</i> ¹⁴	Retrospective analysis	Taiwan	370	676	0.13 (0.09–0.16)	0.13 (0.10–0.16)
Wang <i>et al.</i> ¹³	Prospective analysis	Shanghai	92	397	0.11 (0.05–0.17)	0.11 (0.08–0.14)
Total	NA	NA	1249	630	0.13 (0.10–0.15)	0.12 (0.10–0.14)

Values are given as *n* or mean ± 95% confidence interval. NA, not available.

Table 5 Malignant transformation rate (MTR) of oral leukoplakia (OL) according to lesion site

Site	Wang <i>et al.</i> ¹³		Shi ¹⁵		Gao <i>et al.</i> ¹⁷		Zhu <i>et al.</i> ¹⁶		Lan <i>et al.</i> ⁶		Lee <i>et al.</i> ¹⁴	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Tongue									21	20	65	24.9
Dorsal	4	4.60	2	6.90	24	28.24	1	3.03				
Lateral/ventral	42	19.72	22	25.58	24	28.24	7	14.89				
Total	46	24.32	24	32.48	48	56.48	8	17.92				
Floor of mouth	0	0	1	4.20	2	2.35	6	24.19				
Buccal mucosa	15	6.91	4	5.60	26	30.59			31	10.2	59	8.93
Lip	1	1.96	2	13.30	1	1.18					11	8.8
Palate	1	0.96	1	3.70	2	2.35						
Gingiva	3	3.80	–	–	6	7.06						

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

Table 6 Malignant transformation rate (MTR) of oral leukoplakia (OL) according to age

Study	Study type	City	Age (years)(mean or mean \pm standard deviation)	Age group (years) with the highest MTR
Wang <i>et al.</i> ¹³	Prospective analysis	Shanghai	55.3 \pm 12.6	41–60
Shi ¹⁵	Prospective analysis	Shanghai	53.4	–
Ge <i>et al.</i> ³	Retrospective analysis	Beijing	57.5	50–59
Lee <i>et al.</i> ¹⁴	Retrospective analysis	Taiwan	–	\geq 50
Gao <i>et al.</i> ¹⁷	Retrospective analysis	Beijing	56.0	–

MTR than were younger patients (odds ratio = 2.03; 95% CI = 1.11–3.72)¹⁴. 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 80 years of age had a much higher MTR than did women over 80 years of age¹³.

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^{7–10, 18–20}. This finding is similar to that reported in other published studies outside China^{21,22}. 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 idiopathic¹¹. Schepman *et al.*²³ and Silverman *et al.*²⁴ 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 women¹³.

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^{24,25}; 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 frequently⁷.

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^{11,26}. Shiu found that the correlative risk of OL associated with BQ chewing was 17.7, while 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 OL¹¹. A retrospective study showed that BQ chewers might have a higher chance of developing OL (0.1–0.5% for OL; 0.02–0.05% for oral cancer)²⁷. 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 transformation¹⁴.

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% (32/196) in drinkers *versus* 14.29% (12/84) in non-drinkers²⁸. 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 cancer²⁹. For example, a case-control study in the UK showed that alcohol was linked to smoking as one of the risk factors for dysplasia^{26,30}.

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

Study	Individuals						Pooled MTR			
	Homogeneous			Non-homogeneous			Non-homogeneous			
	Speckled	Granular	Verrucous	Speckled	Granular	Verrucous	Speckled	Granular	Verrucous	Total
Lan <i>et al.</i> ⁶	302	32	38	0.07 (0.05-0.12)	0.22 (0.11-0.39)	0.18 (0.09-0.34)	0.40 (0.26-0.57)	0.22 (0.11-0.39)	0.18 (0.09-0.34)	0.27 (0.19-0.36)
Lee <i>et al.</i> ¹⁴	421	78	113	0.07 (0.05-0.10)	0.32 (0.22-0.43)	0.24 (0.17-0.32)	0.19 (0.15-0.22)	0.32 (0.22-0.43)	0.24 (0.17-0.32)	0.21 (0.18-0.24)
Shi ¹⁵	193	6	17	0.12 (0.07-0.17)	0.33 (0.08-0.73)	0.06 (0.01-0.32)	0.37 (0.19-0.60)	0.33 (0.08-0.73)	0.06 (0.01-0.32)	0.24 (0.11-0.37)
Zhu <i>et al.</i> ¹⁶	117	12	11	0.01 (0.00-0.06)	0.58 (0.31-0.82)	0.28 (0.09-0.59)	0.30 (0.10-0.62)	0.58 (0.31-0.82)	0.28 (0.09-0.59)	0.39 (0.23-0.56)
Total	1033	128	179	0.07 (0.05-0.12)	0.33 (0.22-0.47)	0.22 (0.17-0.29)	0.30 (0.17-0.46)	0.33 (0.22-0.47)	0.22 (0.17-0.29)	0.25 (0.19-0.31)

Values are given as *n* or mean ± 95% confidence interval.

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^{31,32}. The buccal mucosa, which was commonly recognised as the most frequent site of OL³³, had a much lower MTR^{31,34}. However, Lee *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^{23,35}. Such a discrepancy might be the result of differences in oral habits and other local risk factors¹².

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^{34,36}. Lan *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 ($P = 0.013$)². The higher MTR in older patients might suggest that the longer the exposure to OL, the higher the occurrence of malignant transformation^{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^{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 dysplasia³⁹.

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 hyperplasia¹⁷. However, other authors found no relationship between epithelial dysplasia and malignant transformation⁴⁰, probably because in cases of leukoplakia with moderate or severe dysplasia, the lesion was often immediately excised after biopsy¹².

This review is the first to analyse systemically 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

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^{12,41,42}; 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.

REFERENCES

- Dai CA, Fu GC. Oral leukoplakia: etiological analysis, clinical pathology, prevention, therapy. *Chin J Stomatol* 1964 10: 316–319.
- Lan AX, Guan XB, Sun Z. Analysis of risk factors for carcinogenesis of oral leukoplakia. *Chin J Stomatol* 2009 44: 327–331.
- Ge HB, Sun Z, Shen SL. A clinical analysis of 211 oral leukoplakia. *Beijing J Stomatol* 1999 3: 11–12.
- Guan XB, Sun Z, Wang JB. Preliminary study on the relationship between smoking, malignant transformation of oral leukoplakia. *Beijing J Stomatol* 2001 3: 123–124.
- Axell T, Pindborg JJ, Smith CJ et al. Oral white lesions with special reference to precancerous, tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18–21 1994. International Collaborative Group on Oral White Lesions. *J Oral Pathol Med* 1996 25: 49–54.
- Yang SW, Wu CJ, Lee YS et al. Postoperative recurrence as an associated factor of malignant transformation of oral dysplastic leukoplakia. *ORL J Otorhinolaryngol Relat Spec* 2010 72: 280–90.
- Abidullah M, Kiran G, Gaddikeri K et al. Leukoplakia - review of a potentially malignant disorder. *J Clin Diagn Res* 2014 8: ZE01–4.
- Brouns ER, Baart JA, Bloemena E et al. The relevance of uniform reporting in oral leukoplakia: definition, certainty factor, staging based on experience with 275 patients. *Med Oral Patol Oral Cir Bucal* 2013 1: 19–26.
- Neville BW, Damm DD, Allen CM et al. *Oral Maxillofacial Pathology*. Philadelphia: W B Saunders 2002 25: 218–219.
- Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature, classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med* 2007 36: 575–580.
- Shiu MN, Chen TH. Impact of betel quid, tobacco, alcohol on three-stage disease natural history of oral leukoplakia, cancer: implication for prevention of oral cancer. *Eur J Cancer Prev* 2004 13: 39–45.
- Amagasa T, Yamashiro M, Uzawa N. Oral premalignant lesions: from a clinical perspective. *Int J Clin Oncol* 2011 16: 5–14.
- Wang YF, Shang S, Zhou ZT et al. A retrospective analysis on the malignant transformation rate, time, risk factors of oral leukoplakia. *Shanghai J Stomatol* 2011 20: 55–61.
- Lee JJ, Hung HC, Cheng SJ et al. Carcinoma, dysplasia in oral leukoplakias in Taiwan: prevalence, risk factors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006 101: 472–480.
- Shi HB. Analysis of malignancy change of Oral Leukoplakia. *Shanghai J Stomatol* 1992 01: 63–65+129.
- Zhu QS, Miao QA, Zhi KQ et al. A clinical analysis of 150 oral leukoplakia. *J Clin Stomatol* 2009 05: 311–312.
- Gao Y, Guo ZL, Luo HY et al. Clinicopathological characteristics of malignant transformation in 85 cases of oral leukoplakia. *Chin J Stomatol* 2012 47: 410–413.
- Hogewind WF, Van der Waa I, Van der Kwast WA et al. The association of white lesions with oral squamous cell carcinoma. A retrospective study of 212 patients. *Int J Oral Maxillofac Surg* 1989 18: 163–164.
- Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005 55: 74–108.
- Warnakulasuriya S. Global epidemiology of oral, oropharyngeal cancer. *Oral Oncol* 2009 45: 309–316.
- Roed-Petersen B. Cancer development in oral leukoplakia: Follow-up of 331 patients. *J Dent Res* 1971 50: 711–716.
- Rodriguez-Perez I, Banoczy J. Oral leukoplakia. A histopathological study. *Acta Morphol Acad Sci Hung* 1982 4: 289–298.

23. Schepman KP, Van der Meij EH, Smeele LE *et al.* Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncol* 1998 34: 270–275.
24. Silverman S, Bhargava K, Smith LW *et al.* Malignant transformation, natural history of oral leukoplakia in 57,518 industrial workers of Gujarat, India. *Cancer* 1976 38: 1790–1795.
25. Gupta PC, Daftary DK. Epidemiologic, histologic study of oral cancer, leukoplakia among 50,915 villagers in India. *Cancer* 1969 24: 832.
26. Jaber MA, Porter SR, Gilthorpe MS *et al.* Risk factors for oral epithelial dysplasia—the role of smoking, alcohol. *Oral Oncol* 1999 35: 151–156.
27. Xiao-lin Z, Reichart PA. A review of betel quid chewing, oral cancer, precancer in Mainland China. *Oral Oncol* 2007 43: 424–430.
28. Liu W, Shi LJ, Wu L *et al.* Oral cancer development in patients with leukoplakia-clinicopathological factors affecting outcome. *PLoS ONE* 2012 7: 73.
29. Hashibe M, Sankaranarayanan R, Thomas G *et al.* Alcohol drinking, body mass index, the risk of oral leukoplakia in an Indian population. *Int J Cancer* 2000 88: 129–134.
30. Jaber MA, Porter SR, Scully C *et al.* The role of alcohol in non-smokers, tobacco in non-drinkers in the aetiology of oral epithelial dysplasia. *Int J Cancer* 1998 77: 333–336.
31. Schell H, Schönberger A. Zur Lokalisationshäufigkeit von benignen und präkanzerösen Leukoplakien und von Karzinomen in der Mundhöhle. H+ G. *Zeitschrift für Hautkrankheiten* 1987 62: 798–804.
32. Waldron CA, Shafer WG. Leukoplakia revisited. A clinicopathologic study 3256 oral leukoplakias. *Cancer* 1975 36: 1386–1392.
33. Zhang X, Li C, Yi S *et al.* Oral leukoplakia in China: a review. *Oral Maxillofac Surg* 2010 14: 195–202.
34. Banoczy J. Follow-up studies in oral leukoplakia. *J Maxillofac Surg.* 1977 5: 69–75.
35. Lumerman H, Freedman P, Kerpel S. Oral epithelial dysplasia, the development of invasive squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodont* 1995 79: 321–329.
36. Amagasa T, Yamashiro M, Ishikawa H. Oral leukoplakia related to malignant transformation. *Oral Science International* 2006 3: 45–55.
37. Pindborg JJ, Jolst O, Renstrup G *et al.* Studies in oral leukoplakia: a preliminary report on the period prevalence of malignant transformation in leukoplakia based on a follow-up study of 248 patients. *J Am Dent Assoc* 1968 76: 767–771.
38. Silverman S, Gorsky M, Lozada F. Oral leukoplakia, malignant transformation. A follow-up study of 257 patients. *Cancer* 1984 53: 563–568.
39. Chang KW, Lin SC, Kwan PC *et al.* Association of aberrant p53, p21WAF1 immunoreactivity with the outcome of oral verrucous leukoplakia in Taiwan. *J Oral Pathol Med* 2000 29: 56–62.
40. Holmstrup P, Vedtofte P, Reibel J *et al.* Long-term treatment outcome of oral premalignant lesions. *Oral Oncol* 2006 42: 461–474.
41. Gassenmaier A, Hornstein OP. Presence of human papillomavirus DNA in benign, precancerous oral leukoplakias, squamous cell carcinomas. *Dermatology* 1988 176: 224–233.
42. Miller CS, Johnstone BM. Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis, 1982-1997. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodont* 2001 91: 622–635.

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