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Malignant transformation of oral submucous fibrosis in Taiwan: A nationwide population-based retrospective cohort study

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Background: Oral submucous fibrosis (OSF) is one of the well-recognized oral potentially malignant disorders. In this study, we investigated the malignant transformation of OSF in a 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 OSF cohort according to age, sex, and index year. Oral leukoplakia (OL) was further stratified to evaluate for the possible synergistic effects of OSF-associated malignant transformation.

Results: In this cohort, 71 (9.13%) of 778 cases of OSF were observed to transform into oral cancer. The malignant transformation rate was 29.26-fold in the OSF cohort than in the comparison cohort after adjustment (95% confidence intervals 20.55-41.67). To further stratify with OL, OSF with OL (52.46%; 95% confidence intervals 34.88-78.91) had higher risk of malignant transformation rate than OSF alone (29.84%; 95% confidence intervals 20.99-42.42). The Kaplan-Meier plot revealed the rate free of malignant transformation was significant over the 13-year follow-up period (log-rank test, $P<.001$). The mean duration of malignant transformation was 5.1, 2.7, and 2.2 years for non-OSF, OSF alone, and OSF with OL, respectively.

Conclusion: Oral submucous fibrosis patients exhibited a significantly higher risk of malignant transformation than those without OSF. OL could enhance malignant transformation in patients with OSF.

KEYWORDS
cohort study, malignant transformation, nationwide population, oral submucous fibrosis

1 | INTRODUCTION

Oral potentially malignant disorders (OPMDs) have been shown as a likely definition for a predisposition to malignant transformation in oral and oropharyngeal mucosa.[1] Oral submucous fibrosis (OSF) is a well-recognized OPMD, predominantly in the countries of South and South-East Asia.[2] Histopathologically, OSF is characterized by fibrosis, which affects the oral cavity, pharynx, and upper third of the esophagus. The habit of betel quid (BQ) chewing is the major cause for OSF.[3]

Clinically, most cases of oral cancer are preceded by clinically evident oral potentially malignant disorders. As OSF is a disease with high morbidity, it is important to prevent malignant transformation for patients diagnosed with OSF. In India, the malignant

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transformation rate of OSF was ranged from 2.6% to 7.6%.[4,5] Recently, the two case-control studies conducted in Mainland China demonstrated that there were 15%[6] and 11.02%[7] OSF patients developing into oral cancer. The malignant transformation rate of OSF was about 1.9%[8] and 3.72%[9] in two hospital-based follow-up observation studies in southern Taiwan, respectively. A register-based study in Taiwan demonstrated the malignant transformation rate of OSF was up to 8.63% in an oral precancerous lesions cohort.[10]

However, the nationwide population-based study to determine the malignant transformation of OSF is sporadic. In this study, we investigated the retrospective cohort study using the latest version of National Health Insurance (NHI) program of Taiwan to evaluate the rate and time to malignant transformation of OSF in a nationwide population. In addition, the OPMDs including oral leukoplakia (OL) and lichen planus were further stratified to evaluate for their role in malignant transformation of OSF.

2 | MATERIALS AND METHODS

2.1 | Data sources

Taiwan's NHI is a single-payer national program launched in 1995, and the NHI Research Database (NHIRD) maintains the records of the number of cases, treatment patterns, and medical claims reported to the NHI for reimbursement. This insurance program has provided health care up to 99.9% of whole population in 2014.[11]

With the approval from Institutional Review Board at the Chung Shan Medical University Hospital, the Longitudinal Health Insurance Database 2010 (LHID2010) was used for this cohort study. The LHID2010 contains data of original claims of one million beneficiaries randomly selected the year 2010 Registry of Beneficiaries of the NHI program. The demographic data, dates of clinical visits, diagnostic codes, prescription details, expenditures, and registration files were included in this data subset.[12] The International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) was used to identify the patients' diseases.

2.2 | Study population

We identified ambulatory patients for dental visit with newly diagnosed OSF (ICD-9-CM code: 528.8) from 2001 to 2012 as the OSF group, with the date of OSF 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 ≤1 year were excluded. The non-OSF cohort patients were randomly identified from the LHID2000 during the same period, without a history of OSF at a ratio of 1:56 and frequency-matched based on age (at 5-year intervals), sex, and index year with the patients in the OSF group. The exclusion criteria were the same for both groups. The OPMDs with specific ICD-9-CM code oral leukoplakia (OL) (codes: 528.6) and lichen planus (codes: 697.0) simultaneously diagnosed with OSF were further evaluated for the possible synergistic effects of OSF-associated malignant transformation.

2.3 | 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 diagnosis, withdrawal from the insurance system, death, or December 31, 2013, whichever occurred first. The Charlson comorbidity index[13] derived for each individual in the cohort diagnosed before the index date was analyzed. The Charlson score was categorized as follows: 0, 1, 2, and ≥3 with higher scores indicating higher comorbidity.

2.4 | Statistical analysis

Demographic factors including age, sex, and comorbidities were compared between the two groups. Chi-squared tests were used to examine the differences in the sex and comorbidity distributions. Student's t-tests were used to examine the differences of mean age between the two 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

TABLE 1 Demographic data of matched study cohorts

	OSF (N=778)		Non-OSF (N=43568)		
	n	%	n	%	*P*-value
Age					
18-34	241	31.0	13021	29.9	.724
35-49	322	41.4	18014	41.3	
50-64	215	27.6	12533	28.8	
Mean ± SD	41.8 ± 11.7		42.1 ± 11.9		
Gender					
Female	100	12.9	5671	13.0	.893
Male	678	87.1	37897	87.0	
Monthly income					
<NT $20,000	329	42.3	18294	42.0	.666
NT $20,000-NT $40,000	309	39.7	16890	38.8	
>NT $40,000	140	18.0	8384	19.2	
CCI[a]					
0	547	70.3	31577	72.5	.401
1	199	25.6	10373	23.8	
≥2	32	4.1	1618	3.7	
Hypertension	116	14.9	5752	13.2	.164
Hyperlipidemia	89	11.4	4088	9.4	.052
Oral leukoplakia	191	24.6	29	0.1	<.001*
Lichen planus	2	0.3	5	0.01	.006*

[a]Charlson comorbidity index.
*P<.01.

controlling variables with a significant difference in crude model. The statistically significant level was set at P value <.05. All statistical analyses were performed with the SPSS version 19 (SPSS, Chicago, IL, USA).

3 | RESULTS

The OSF group comprised 778 patients with newly diagnosed OSF from 2000 to 2012, whereas the non-OSF group comprised 43568 controls without OSF from 2000 to 2012 with similar sex and age distributions (Table 1). Patients with OSF were predominantly men (87.1% vs 12.9%) with a mean age of 41.8 years (standard deviation±11.7). There are no significant changes for among age, gender, urbanization, monthly income, Charlson comorbidity index, hypertension, and hyperlipidemia (P>.05). However, OSF with OL (24.6%) was higher than in comparisons with individuals without OSF (0.1%) for oral cancer development. As shown in Table 1, only two cases involving oral lichen planus were extracted from LHID2010. Therefore, only OL was further analyzed in OSF cohort.

Table 2 presents the risk of oral cancer stratified by OSF, age, gender, monthly income, CCI, hypertension, and hyperlipidemia in Cox proportional hazard regression. The malignant transformation rate of this cohort of 778 patients with OSF was 9.13% (71/778). In addition, patients with OSF had a higher risk of oral cancer as compared to non-OSF group (adjusted HR: 29.26; 95% CI: 20.55-41.67). The age-specific adjusted HR of oral cancer in patients with OSF increased with age from 5.22 (age, 35-49 years) to 6.20 (age, 50-64 years). Male group had higher malignant transformation risk than female (adjusted HR: 14.53; 95% CI: 3.60-58.64). Higher monthly income group has lower risk of oral cancer (adjusted HR: 0.36; 95% CI: 0.22-0.58). However, there was no significant risk of oral cancer with CCI, hypertension, and hyperlipidemia in the adjusted model. Patients with OL had a highest risk of oral cancer (adjusted HR: 1.85; 95% CI: 1.15-2.96).

Table 3 presents the comparison with the risk of subtype oral cancer development between OSF and non-OSF according to ICD-9 classification. The rank orders with respect to the range of HR were found to be as follows: lip > gum > other and unspecified parts of mouth> oropharynx> tongue> other and ill-defined sites within the lip, oral cavity, and pharynx. The highest incidence density was 14.7 cases per 1 000 person-years in subtype of other and unspecified parts of mouth (ICD-9-CM code: 145).

The risk of malignant transformation stratified by OSF and OL in Cox proportional hazard regression is shown in Table 4. Patient with OSF had higher malignant transformation than non-OSF group (adjusted HR: 29.84; 95% CI: 20.99-42.42). Moreover, the risk of malignant transformation in patient both with OSF and OL was up to

TABLE 2 Risk factor analysis of oral cancer development

	No. of oral cancer event	Observed person-years	ID	Crude HR	95% CI		Adjusted HR	95% CI	
					Lower	Upper		Lower	Upper
OSF									
No	123	281338	0.4	1			1		
Yes	71	4674	15.2	34.68**	25.89	46.44	29.26**	20.55	41.67
Age									
18-34	18	96575	0.2	1			1		
35-49	105	114660	0.9	4.91**	2.98	8.10	5.07**	3.06	8.42
50-64	71	74777	0.9	5.10**	3.04	8.55	5.89**	3.44	10.11
Gender									
Female	2	38765	0.1	1			1		
Male	192	247247	0.8	15.04**	3.73	60.57	14.53**	3.60	58.64
Monthly income									
<NT $20,000	90	125261	0.7	1			1		
NT $20,000-NT $40,000	84	105823	0.8	1.10	0.82	1.49	0.93	0.69	1.26
≥NT $40,000	20	54929	0.4	0.51**	0.31	0.82	0.36**	0.22	0.58
CCI									
0	138	210911	0.7	1			1		
1	48	66185	0.7	1.11	0.80	1.54	0.78	0.54	1.12
≥2	8	8917	0.9	1.36	0.67	2.78	0.89	0.42	1.89
Hypertension	36	32250	1.1	1.79**	1.24	2.57	1.05	0.70	1.59
Hyperlipidemia	26	21769	1.2	1.87**	1.24	2.83	1.47	0.92	2.36
Oral leukoplakia	30	1125	26.7	46.10**	31.22	68.08	1.85*	1.15	2.96

CCI, Charlson comorbidity index; ID: incidence density, per 1000 person-years
*P<.05; **P<.01.

TABLE 3 Subtype analysis of oral cancer development between OSF and non-OSF

	OSF			Non-OSF				95% CI	
	No. of event	Observed person-years	ID	No. of event	Observed person-years	ID	HR[a]	Lower	Upper
Lip	13	4918	2.6	23	281621	0.1	39.35	19.13	80.96
Tongue	21	4915	4.3	56	281534	0.2	22.32*	12.63	39.46
Gum	16	4931	3.2	28	281614	0.1	37.58*	19.05	74.12
Other and unspecified parts of mouth[b]	69	4692	14.7	97	281389	0.3	34.75*	24.04	50.23
Oropharynx	13	4949	2.6	28	281628	0.1	24.66*	11.24	54.09
Other and ill-defined sites within the lip, oral cavity, and pharynx[b]	6	4957	1.2	14	281648	0.05	22.29*	7.34	67.66

ID, Incidence density, per 1000 person-years.
[a]Adjusted for age, gender, monthly income, Charlson comorbidity index, hypertension, hyperlipidemia, and oral leukoplakia.
[b]Adjusted for age, monthly income, Charlson comorbidity index, hypertension, hyperlipidemia, and oral leukoplakia (excluded gender variable, because of none event of female data).
*$P<.01$

TABLE 4 Hazard ratios of oral cancer development between oral submucous fibrosis and oral leukoplakia

	N	No. of oral cancer event	Crude HR	95% CI		Adjusted HR[a]	95% CI	
				Lower	Upper		Lower	Upper
Group								
Non-OSF	43568	123	1			1		
OSF alone	587	42	26.08*	18.37	37.02	29.84*	20.99	42.42
OSF and OL	191	29	66.44*	44.30	99.62	52.46*	34.88	78.91

[a]Adjusted for age, gender, monthly income, Charlson comorbidity index, hypertension, and hyperlipidemia.
*$P<.01$.

52.46 (95% CI: 34.88-78.91). As shown in Figure 1, the rate free of malignant transformation estimated using Kaplan-Meier analysis was significant over the 13-year follow-up period (log-rank test, $P<.001$).

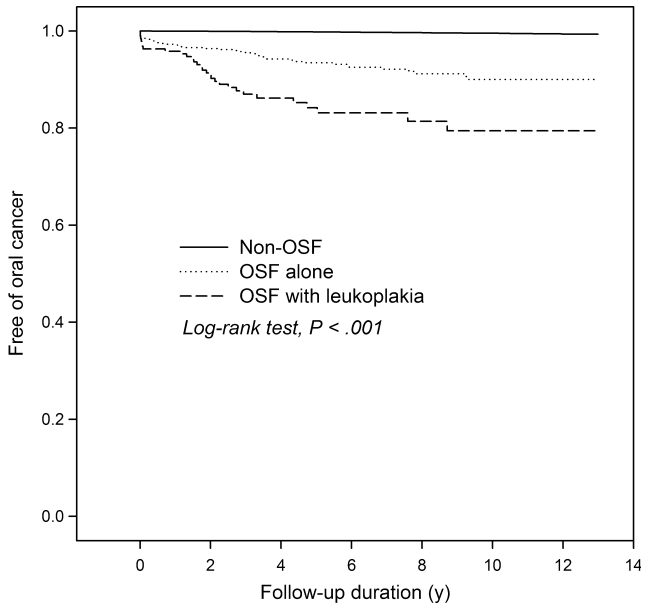

FIGURE 1 The Kaplan-Meier plot for the rate free of malignant transformation over the 13-year follow-up period

The mean follow-up duration and time to malignant transformation between OSF and non-OSF are shown in Table 5. A total of 194 patients (123 non-OSF and 71 OSF patients) underwent malignant transformation to oral cancers in this cohort. The malignant transformation rate of OSF was 9.13%. The mean duration of malignant transformation was 5.1 years and 2.5 years for non-OSF and OSF groups, respectively. To further stratify by OSF group, the mean duration of malignant transformation was 2.7 and 2.2 years for OSF alone and OSF with OL, respectively.

4 | DISCUSSION

In this population-based longitudinal study examining the malignant transformation of OSF in Taiwan, there was a 29.26-fold increased risk of developing into oral cancer witnessed in OSF cohort than in

TABLE 5 Mean follow-up duration and time to malignant transformation between OSF and non-OSF

	Follow-up duration (years)			Time to event (years)		
	N	Mean	SD	N	Mean	SD
Non-OSF	43568	6.5	3.6	123	5.1	3.2
OSF	778	6.0	3.7	71	2.5	2.5
OSF alone	587	6.3	3.6	42	2.7	2.7
OSF and OL	191	5.2	3.6	29	2.2	2.2

non-OSF cohort. The risk of malignant transformation was higher in male patients as well as in lower income group. In addition, the adjusted HR of oral cancer progressively increased with age.

The malignant potential of OSF was first reported by Paymaster in 1956.[14] However, the malignant transformation of OSF still needs further discussion. To our knowledge, this is the most recent nationwide cohort study, which reported that 9.13% OSF patients transformed into malignancies in Taiwan with 13-year follow-up period. The malignant transformation rate of OSF is higher than previous studies (1.9 to 8.63%) in Taiwan.[8-10] In addition, the mean time to malignant transformation is 30 months, which is shorter than 52.3, 65.39, and 37.42 months reported by Hsue et al.,[8] Wang et al.,[9] and Lian et al.,[10] respectively. These may be partly explained by the higher prevalence of OSF in Taiwan significantly increased from 1996 to 2013.[15] In addition, Taiwan government launched an oral cancer pre-screening health promotion program and periodic clinical follow-up owing to awareness. Those persons who are the current/ex-alcohol drinkers/betel quid chewers/cigarette smokers are encouraged to receive oral examination for the possible presentation of OPMDs.

This study also revealed that OSF patients with OL had higher malignant transformation rate and shorter duration than patients with OSF alone. This indicated that OL could play a synergistic effect of malignant transformation in OSF patients. Our results were in agreement with those of Lian et al. [10] who reported that patient with both OSF and OL had higher malignant transformation rate than patient with either OSF alone or patient with OL alone during the observation period between 1988 and 1998 in Taiwan. Thus, the histopathological mechanisms for malignant transformation need to be clarified further. Moreover, the weight for malignant transformation of OSF or OL is worth further analysis.

The strength of this study is the use of nationwide population-based database that provided sufficient sample size, generalizability, and statistical power to assess the malignant transformation of OSF in Taiwan. However, there are still some limitations for this study. First, OSF is believed to be highly associated with BQ chewing habit in Taiwan.[16] The information retrieved from the database did not contain oral habits such as BQ chewing, smoking, and alcohol consumption. However, estimated two million BQ chewers are also smokers or drinkers in Taiwan.[17] Second, the data source of this study was the NHIRD, which lacked relevant clinical findings such as the degree of trismus, trauma from severe attrition, and sharp edges in posterior teeth, chronic trauma to lateral border of tongue. Third, pathological grade of tumor differentiation, clinical TNM stage, and malnutrition were not available in the NHIRD dataset. In this meticulous study design, the possible effects due to confounding bias from above factors might be minimized by adjusting for year, gender, insurance cost, and CCI index. We believe that the results of malignant transformation of oral submucous fibrosis in this study are highly reliable because of the validity of the database, large sample size, and long follow-up periods.

In conclusion, the patients with OSF exhibited a significantly higher risk of malignant transformation than those without OSF. In addition, OL could act as a synergistic effect of OSF-associated malignant transformation. Additional studies are warranted to clarify the histopathology underlying the possible mechanisms of OSF-associated malignant transformation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this study.

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