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Malignant transformation of oral potentially malignant disorders in Taiwan

An observational nationwide population database study

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Abstract

Oral cancer is one of the leading causes of cancer death, which are mostly preceded by oral potentially malignant disorders (OPMDs). Taiwanese government launched a free oral cancer screening program. The aim of this study was to analyze the malignant transformation rate of OPMDs.

This study was based on national-wide oral screening databases. 3,362,232 people were enrolled. Patients clinically diagnosed with leukoplakia, erythroplakia, oral submucosal fibrosis (OSF), oral verrucous hyperplasia (OVH), and oral lichen planus (OLP), from 2010 to 2013, were identified. We followed up OPMD patients in cancer registry databases to analyze the malignant transformation rate.

The malignant transformation rates from the highest to the lowest were: OVH > OSF > erythroplakia > OLP > leukoplakia. The malignant transformation rate was 24.55, 12.76, 9.75, 4.23, and 0.60 per 1000 person-years in the OVH, OSF, erythroplakia, leukoplakia, and comparison cohort. The hazard ratio was 8.19 times higher in the OPMD group compared with comparison cohort group, after age and habit adjustment. Female patients with OPMDs had a high risk of malignant transformation.

Nationwide screening is very important for early diagnosis. OVH had the highest malignant transformation possibility. Female OPMD patients are a rare but have a relatively high malignant transformation rate.

Abbreviations: AJCC = American Joint Committee on Cancer, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, K–M plot = Kaplan–Meier-plotter, NHI = National Health Insurance, OLP = oral lichen planus, OPMD = oral potentially malignant disorder, OSF = oral submucosal fibrosis, OVH = oral verrucous hyperplasia, SCC = squamous cell carcinoma, WHO = World Health Organization.

Keywords: betel nut, erythroplakia, leukoplakia, malignant transformation, oral cancer, oral lichen planus, oral mucosal screening, oral potentially malignant disorders, oral submucosal fibrosis, oral verrucous hyperplasia

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H-KH contributed equally to W-FC.

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This study is the first to rank the malignant transformation rates of OPMD subtypes by using a nationwide database. OVH was the subtype associated with the highest chance of malignant transformation in Taiwan. Early screening for oral cancer and OPMD is crucial and may be lifesaving.

The authors declare that they have no competing interests.

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Oral cancer is the 11th most common cancer in the world,[1] as well as the 4th most frequently occurring cancer and the 5th leading cause of cancer death in Taiwan.[1] The high frequency of oral cancer in Taiwan may be a result of the high prevalence (16.5% of men) of betel quid chewing habit.[1] The Taiwanese government launched a free oral cancer screening program since 2010 for betel quid chewers and cigarette smokers in hope of lowering oral cancer prevalence. Because most oral cancer cases are preceded by clinically evident oral potentially malignant disorders (OPMDs), being able to identify OPMD and preventing them from malignant transformation is important.[1] The World Health Organization (WHO) recognizes leukoplakia, erythroplakia, oral submucosal fibrosis (OSF), oral verrucous hyperplasia (OVH), and oral lichen planus (OLP) as OPMDs.[1] Overall, approximately 4% of men in the world have OPMDs according to the WHO data.[2]

Nationwide oral cancer screening for high-risk patients is essential for early diagnosis and has the potential to save lives. OPMDs are a group of heterogeneous precancerous lesions associated with various risks of transformation into invasive cancer. The malignant transformation rates of these precancerous lesions are usually related to genetic, geographic, and lifestyle factors. Stratification of OPMD subtypes by malignant transformation rate may facilitate the development of follow-up measures and optimization of treatment strategies, thus limiting malignant transformation. Numerous studies have reported the malignant transformation tendencies of OPMD subtypes. However, no studies have directly ranked the MR rates of all OPMD subtypes in a single nationwide population. Therefore, we investigated the epidemiology of OPMD in Taiwan using nationwide screening databases and ranked the malignant transformation rates of OPMD subtypes.

2. Materials and methods

Taiwan launched the single-payer National Health Insurance (NHI) program on March 1, 1995. NHI offers comprehensive medical care coverage to residents of Taiwan. The program covered 99.5% of the Taiwan's 22.96 million legal residents by 2010.[3–5]

The National Health Insurance Research Database provides data on insurants' gender, date of birth, date of death, and cause of death as well as oral mucosal screening data and cancer registry data, and encrypted patient identification numbers are used to ensure patient privacy.

Data on the cause of death and cancer registry data were obtained using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and ICD-10 codes for diagnoses. The cancer registry uses the American Joint Committee on Cancer (AJCC) TNM system to define cancer severity. Oral mucosal screening data comprise information on clinical diagnosis, biopsy result, follow-up, further treatment condition, smoking, or betel nut chewing history. In Taiwan, every hospital has a coder team to ensure the accuracy of diagnostic and management codes, including codes in the cancer registry. All data set of Taiwan National Health Research Institutes is released with deidentified secondary data for public research. Because all types of personal data are encrypted to ensure patient privacy, the present study was granted an exemption from a full ethical review by the Institutional Review Board of Chi Mei Medical Center. An additional file shows the ethics approval in more detail (for IRB see Supplementary Fig. S1, http://links.lww.com/MD/F800).

2.1. Selection of patients and variables

The oral mucosal screening test was performed by dentists and otolaryngologists. People who underwent screening might be clinically diagnosed with normal results, oral ulcer, erosion, leukoplakia, erythroplakia, OSF, OVH, OLP, or highly suspected to have malignancy. In our study, we characterized the demographics of OPMDs, which includes leukoplakia, erythroplakia, OSF, OVH, and OLP, from 2010 to 2013, from the databases. We include people whose oral screening reports were normal into the comparison cohort, to compare with the OPMD groups. Patients who had clinically diagnosed with OPMDs or highly suspected to have malignancy were referred to hospital to have oral biopsies for histological confirmation. The oral biopsy results included normal result, as well as results of hyperplasia, dysplasia, carcinoma in situ, squamous cell carcinoma (SCC), and verrucous carcinomas. If the histological report confirmed the lesions as malignant or carcinoma in situ, the patient would be excluded from our study. Patients who had malignancy or carcinoma in situ would be referred to a hospital immediately for cancer treatment, and the patients' data will be recorded in the cancer registry database. In our study, we excluded patients who had history of oral cancer before 2010 based on cancer data in the cancer registry database.

We recorded the following demographic factors of OPMD patients: age, smoking status, betel nut chewing status, biopsy, and followed up them until December 31, 2015, to observe the malignant transformation rate of these patients. If an OPMD patient died before the end of the study, we surveyed the autopsy report in death database to evaluate the oral cancer-free interval.

2.2. Statistical analysis

The difference from the average age and the time to oral cancer was derived from *t* test and Pearson's χ^2 test was used for testing the independence of age groups, gender, history of smoking, and betel nut chewing, between OPMD patients and comparison patients. Incidence rate was expressed as number of oral cancers per 1000 person-time in stratum of oral potentially malignant disorders. Cox proportional hazard model analysis was used to investigate the independent predictors of the malignant transformation rate between 2 cohorts. All demographic variables of patients were controlled in the adjusted model.

SAS 9.4 (SAS Institute Inc., Cary, NC) was used for data analyses. Significance was set at $P < .001$ (2-sided).

3. Results

From 2010 to 2013, there were altogether 3,362,232 people that underwent the oral screening test sponsored by the government. After excluding patients who had history of oral cancer, we enrolled 155,103 OPMD patients and 3,145,824 people whose oral screening reports were normal were enrolled as comparison cohort in our study. Figure 1 is the flow chart of this study with details in sample selection and number of cases.

Mean ages were 49.42 years in the OPMD group and 51.50 years in the comparison cohort. In age-stratified analyses, significant differences were observed between the OPMDs and

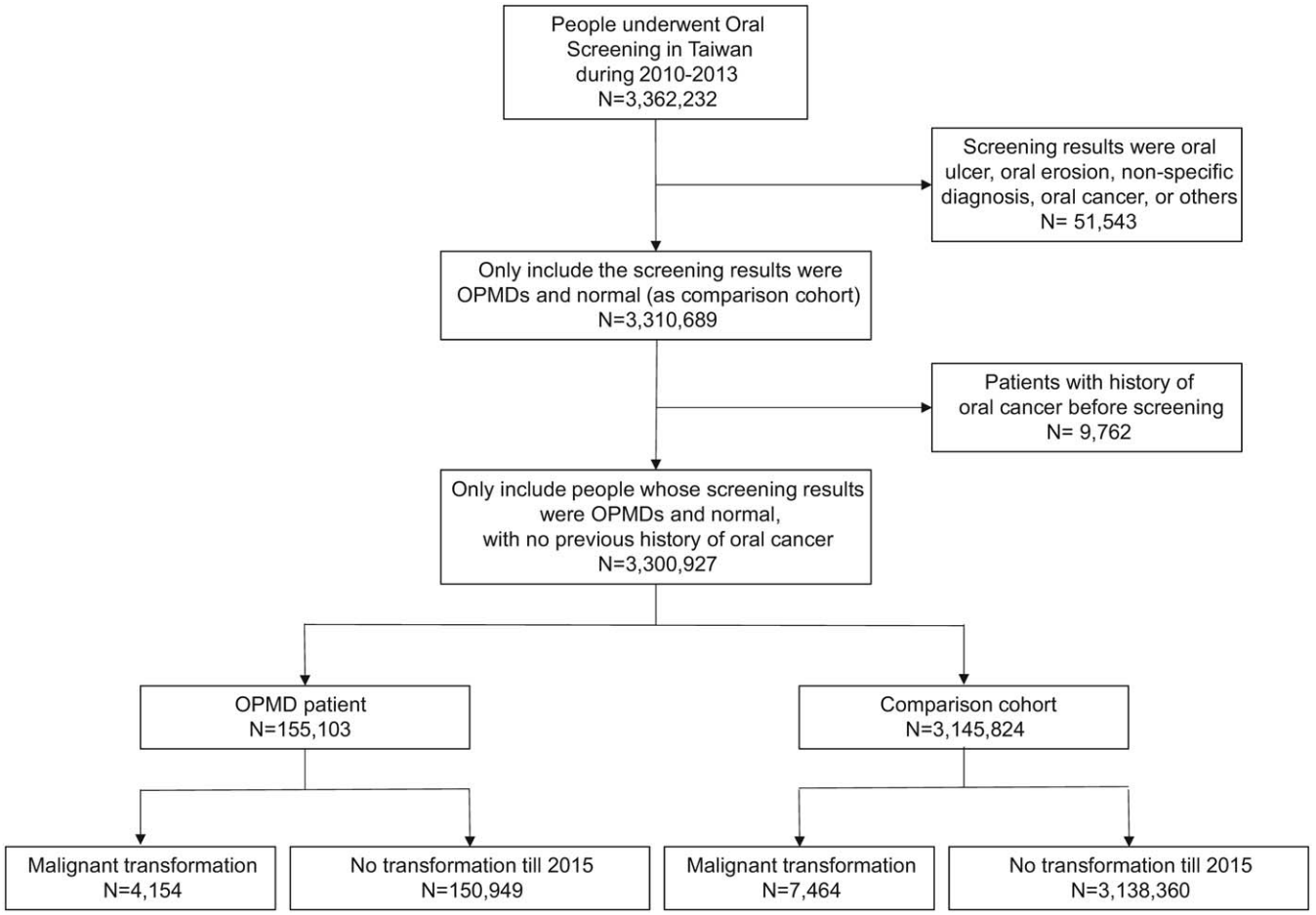


Figure 1. Flow chart of study sample selection. Malignant transformation = a non-malignant case develops into an oral cancer patient, OPMDs = oral potentially malignant disorders.

comparison cohort ($P < .0001$). There is a significantly higher percentage of men in the OPMD group than that in the comparison cohort (94.68% vs 73.96%, $P < .0001$). Although all people who received oral mucosal screening had a history of smoking or betel nut chewing, the smoking and betel nut chewing rates were still significantly higher in the OPMD group (smoking: 94.63% vs 87.79%, $P < .0001$; betel nut chewing: 75.18% vs 51.97%, $P < .0001$). The malignant transformation rate was significantly higher in the OPMD group than in the comparison cohort as well (2.68% vs 0.24%, $P < .0001$). Moreover, the malignant transformation time was shorter in the OPMD group (1.82 ± 1.55 years vs 2.10 ± 1.47 years). The detailed results are shown in Table 1.

In Table 2, the risk of malignant transformation between the OPMDs and comparison cohort groups is presented in terms of the Cox proportional hazard ratio (HR). Although all OPMD lesions had been proven to exhibit precancer statuses, malignant transformation potentials were different among the subtypes of OPMDs. Based on the malignant transformation rates, all OPMDs could be ranked as follows: OVH (9.40%) > OSF (5.03%) > erythroplakia (3.91%) > OLP (1.77%) > leukoplakia (1.68%). The annual malignant transformation rate is shown in Table 3. The malignant transformation rate as per 1000 person-years was 24.55 for OVH, 12.76 for OSF, 9.75 for erythroplakia, 4.23 for leukoplakia, 4.20 for OLP, and 0.60 for comparison cohort. Table 3 also provided a comparison of age, gender, and habits between the OPMD group and the comparison cohort.

To clarify the risk and association of malignant transformation, we adjusted for potential confounding factors such as age, gender, betel nut chewing, and smoking history. The men in the

Table 1

Demographic information of OPMDs and comparison cohort.

	OPMDs N = 155,103	Comparison cohort N = 3,145,824	*P*
Age (Mean ± SD)	49.42 ± 11.69	51.50 ± 14.27	<.0001
Age groups			
40≦	39,430 (25.42)	835,370 (26.55)	<.0001
40–60	89,403 (57.64)	1,497,163 (47.59)	
60>	26,270 (16.94)	813,291 (25.85)	
Gender			
Male	146,859 (94.68)	2,326,753 (73.96)	<.0001
Female	8244 (5.32)	819,071 (26.04)	
Betel nut chewer	116,606 (75.18)	1,629,170 (51.79)	<.0001
Smoker	146,771 (94.63)	2,761,609 (87.79)	<.0001
Malignant transformation	4154 (2.68)	7464 (0.24)	<.0001
Time to cancer (yr), Mean ± SD	1.82 ± 1.55	2.10 ± 1.47	<.0001

Comparison cohort = people whose oral screening reports were normal were included into the comparison cohort in this study, Malignant transformation = a non-malignant case develop into an oral cancer patient, OPMD = oral potentially malignant disorder.

Table 2

Malignant transformation rate and cases in OPMDs.

	Malignant transformation	
OPMDs, number (%)	Oral cancer N = 11,594	Rate*
OVH	488 (9.40)	24.55
OSF	1208 (5.03)	12.76
Erythroplakia	587 (3.91)	9.75
Leukoplakia	1833 (1.68)	4.23
OLP	36 (1.77)	4.20
Comparison cohort	7442 (0.24)	0.60

Comparison cohort = people whose oral screening reports were normal were included into the comparison cohort in this study, Malignant transformation = a non-malignant case develop into an oral cancer patient, OLP = oral lichen planus, OPMD = oral potentially malignant disorder, OVH = oral verrucous hyperplasia, OSF = oral submucosal fibrosis.

* Rate: Malignant transformation rate per 1000 person-years.

OPMD group had a higher risk of malignant transformation than those in the comparison cohort before and after adjustment (crude HR: 9.18 [95% CI: 8.84–9.55], adjusted HR: 7.94 [7.63–8.26]). Women in the OPMD group had an especially higher risk of malignant transformation than those in the comparison cohort before and after adjustment (crude HR: 22.41 [18.22–27.56], adjusted HR: 21.14 [17.17–26.02]).

People who chewed betel nut in the OPMD group had higher malignant transformation risk than those in the comparison cohort group before and after adjustment (crude HR: 9.33 [8.94–9.73], adjusted HR: 8.18 [7.83–8.54]).

People who smoked in the OPMD group had higher malignant transformation risk than those in the comparison cohort group before and after adjustment (crude HR: 10.58 [10.17–11.00], adjusted HR: 7.89 [7.58–8.22]).

In Figure 2, based on the prevalence rates, all OPMDs could be ranked as follows: leukoplakia > OSF > erythroplakia > OVH > OLP, during the study period, from 2010 to 2013.

Figures 3 and 4 showed the Kaplan–Meier-plotter (K–M plot) of the cumulative malignant transformation incidence in OPMD group, and in the comparison cohort, and cumulative incidence among each OPMDs. Figures 3 and 4 also provided the case that were at risk upon being diagnosed and during the follow-up period in our study. Figure 3 showed that the OPMD group had a higher probability of developing oral cancer than the comparison. Furthermore, from the K–M plot in Figure 4, we can see that the time of malignant transformation of OLP is earlier than that of the other OPMD types.

4. Discussion

4.1. Government policy

To our knowledge, there exists no large national research on OPMDs so far, because most countries did not have screening programs for OPMDs. The screening program launched in Taiwan is a government policy, which enables us to perform this unique research with the largest number of OPMD cases up to dates.

4.2. Risk comparison between All OPMDs

Based on the prevalence rates, all OPMDs could be ranked as follows: leukoplakia > OSF > erythroplakia > OVH > OLP, from 2010 to 2013 (Fig. 2). According to our study results, the malignant transformation rates from the highest to the lowest were as follows: OVH > OSF > erythroplakia > OLP > leukoplakia (Table 2). Previous studies in Taiwan have shown the same sequence of malignant transformation: OVH > OSF > OLP.[1] A study in Sweden[6] also ranked the malignant transformation rate as follows: OSF > OLP. We are the first research to include all 5 types of OPMD cases, compared to the only 1 or 2 OPMD types research done in previous research.

4.3. OVH

In this study, the malignant transformation rate of OVH was the highest in Taiwan, with 9.40% of OVH transformed into oral squamous carcinoma and/or verrucous carcinoma. Our result is only compatible with a previous studies at a single medical center in Southern Taiwan,[1] which reveals that 6.79% of OVH transformed into oral cancers; 5.06% and 1.73% of oral cancers were SCC and verrucous carcinomas, respectively. A 5-year study reported that 10% cases of OVH were transformed into oral cancers in Taiwan.[7] One small population-based study of Southern Taiwan male patients reported that 52.1 per 1000 OVH patients had malignant transformation per year,[8] which was higher than that in our study (24.55 per 1000 OVH patients per year). However, the risk of malignant transformation in an

Table 3

Risk of malignant transformation between the OPMDs and comparison cohort represented in terms of the Cox proportional hazard ratio.

	OPMDs			Comparison cohort				
	Malignant Transformation	Person-Year	Rate	Malignant Transformation	Person-Year	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)
Overall	4154	617,111.16	6.73	7464	12,434,958.37	0.06	11.20 (10.78–11.63)	8.19 (7.87–8.51)
Age groups								
40≦	519	158,516.65	3.27	692	3,308,348.39	0.21	15.57 (13.89–17.45)	9.82 (8.73–11.05)
40–60	2739	357,268.55	7.67	4562	6,014,648.61	0.76	10.09 (9.62–10.58)	7.21 (6.87–7.57)
60>	896	101,325.95	8.84	2210	3,111,961.37	0.71	12.45 (11.52–13.45)	10.26 (9.48–11.10)
Gender								
Male	4043	584,417.81	6.92	6990	9,287,436.55	0.75	9.18 (8.84–9.55)	7.94 (7.63–8.26)
Female	111	32,693.35	3.40	474	3,147,521.82	0.15	22.41 (18.22–27.56)	21.14 (17.17–26.02)
Betel nut chewer	3589	462,396.70	7.76	5322	6,407,842.52	0.83	9.33 (8.94–9.73)	8.18 (7.83–8.54)
Smoker	281	33,715.52	8.33	6827	10,891,843.11	0.63	10.58 (10.17–11.00)	7.89 (7.58–8.22)

Comparison cohort = people whose oral screening reports were normal were included into the comparison cohort in this study, Malignant transformation = a non-malignant case develops into an oral cancer patient, OPMDs = oral potentially malignant disorders.

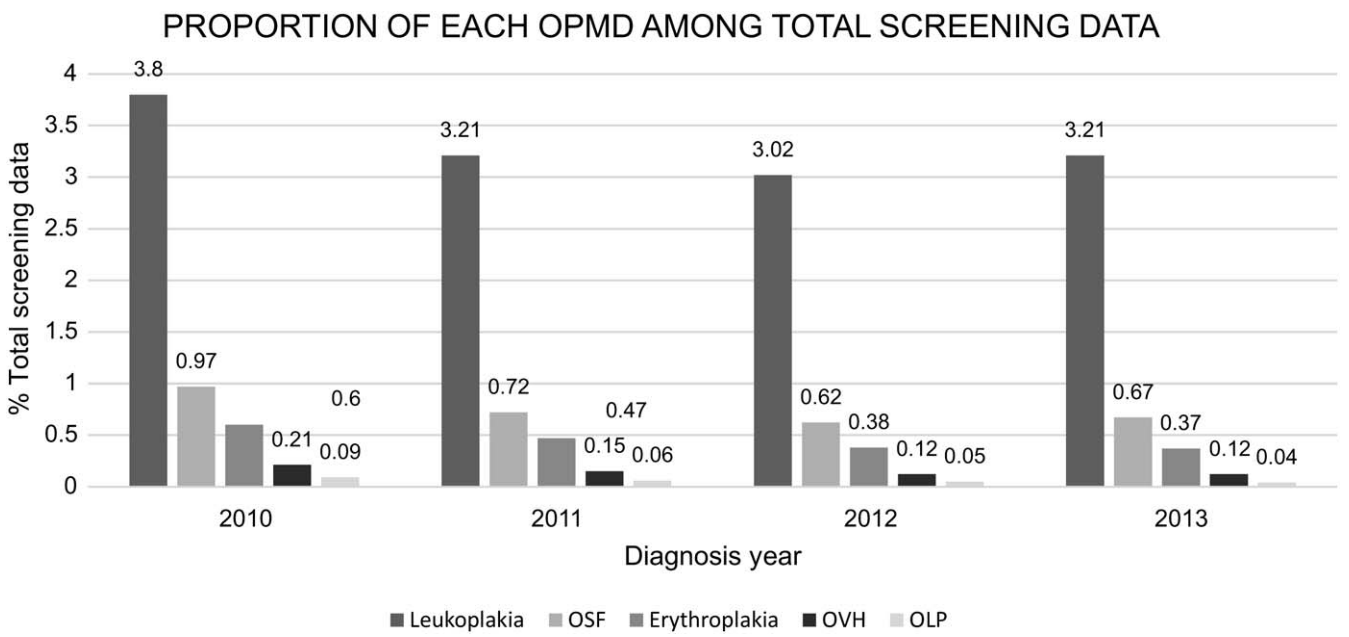
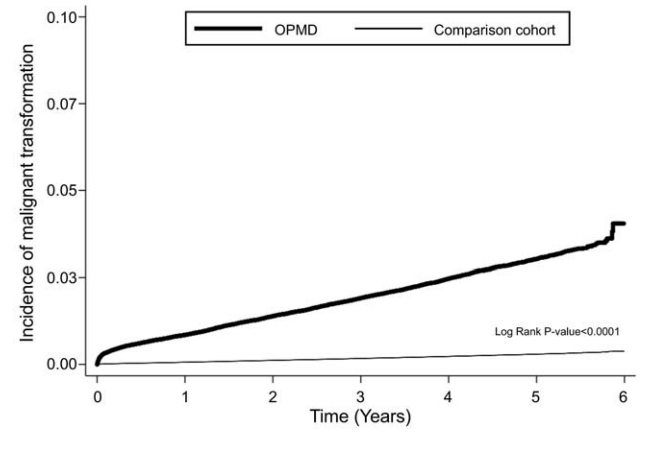


Figure 2. The trends in annual proportion of OPMD patient numbers to the total oral screening case numbers for each OPMD subtypes from 2010 to 2013. OLP = oral lichen planus, OPMDs = oral potentially malignant disorders, OSF = oral submucosal fibrosis, OVH = oral verrucous hyperplasia.

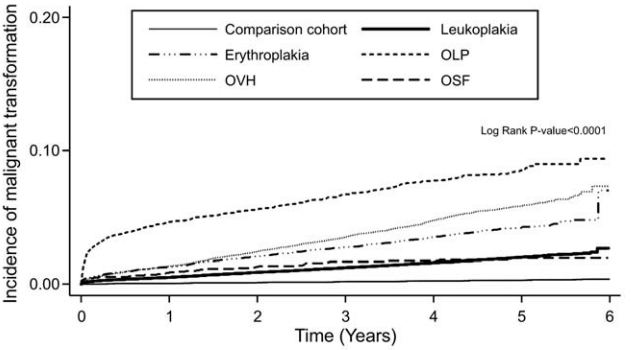
Italian report (approximately 2%–3% for verrucous leukoplakia) is significantly lower than that in a Taiwan report. One potential explanation for this difference is that verrucous leukoplakia is often viewed as a subtype of leukoplakia in the Italian.[9] Another reason for the underestimation of the malignant transformation rate in the previous studies is that they often focused on oral SCC formation; therefore, verrucous carcinoma cases have always been neglected.[9] In our study, oral SCC and verrucous carcinoma were both included. This nationwide population-based study in Taiwan discovered that OVH is the OPMD subtype with the highest malignant transformation rate. Therefore, policy makers should ensure that sufficient resources are provided for patients with OVH in particular. In addition, dentists and otolaryngologists should perform biopsies more aggressively for patients with OVH with a high likelihood of malignancy.



Number at risk

OPMD	155103	151576	148874	118833	82896	40554	-
Comparison cohort	3145824	3111376	3074780	2427508	1601183	704658	-

Figure 3. K–M plot of malignant transformation in the OPMD group and comparison cohort. Comparison cohort = people whose oral screening reports were normal were included into the comparison cohort in this study, K–M plot = Kaplan–Meier-plotter, Malignant transformation = a non-malignant case develop into an oral cancer patient, OPMD = oral potentially malignant disorders.



Number at risk

Comparison cohort	3145824	3111376	3074780	2427508	1601183	704658	-
Leukoplakia	108869	106969	105266	83623	57698	27868	-
Erythroplakia	15007	14552	14253	11656	8407	4181	-
OLP	5190	4800	4690	3829	2750	1409	-
OVH	24000	23254	22688	18046	12776	6407	-
OSF	2037	2001	1977	1679	1265	689	-

Figure 4. K–M plot of malignant transformation in the OPMD subtypes and comparison cohort. Comparison cohort = people whose oral screening reports were normal were included into the comparison cohort in this study, K–M plot = Kaplan–Meier-plotter, Malignant transformation = a non-malignant case develop into an oral cancer patient, OLP = oral lichen planus, OPMD = oral potentially malignant disorders, OVH = oral verrucous hyperplasia, OSF = oral submucosal fibrosis.

4.4. OSF

OSF had the second highest malignant transformation rate in our study. OSF is a chronic condition[1] and is directly associated with the habit of betel nut chewing. Because this habit is more often seen in the Asian population, OSF is predominantly observed among Asian populations.[10]

In our study, 5.03% of OSF patients experienced malignant transformation. A 10-year Asian research has shown the malignant transformation rate to be approximately 1.9% to 10%.[1,11,12] A 17-year study in India has shown that the transformation rate was 7.6% among OSF cases.[13] A Sweden study reported that the transformation rate is 2% to 8%, and the transformation is highly associated with smoking.[6]

4.5. OLP

Some previous studies have indicated that the malignant transformation rate for OLP is very low.[14] This may be because OLP has the lowest association with smoking, alcohol consumption, and betel nut chewing among all OPMDs. In a UK study, the most common OPMD was OLP, and the annual rate of transformation was 3.6 to 7.1 per 1000 people.[15]

The annual malignant transformation rate in our study was 4.20 per 1000 person-years, and the 5-year malignant transformation rate was 1.77%, which is compatible with rate (1.9% in 7-year follow-up) found in a systemic review of OLP.[16] This systemic review describes that female patients suffer from a higher risk of malignant transformation than male patients. In an American study investigating the malignant transformation population (66% of the population were women), 57% of malignant transformation population reported no history of tobacco or alcohol use.[16]

Past research indicates that OLP is not likely to have malignant transformation, and there is no need for close follow-ups. However, according to our research, the K–M plot (Fig. 4.) revealed that although OLP has a low malignant transformation rate, there is a tendency for it to transform early. More data are required to confirm the time interval of malignant transformation from first OLP diagnosis. If further studies reveal that the malignant transformation of OLP is earlier than those of other OPMD subtypes, then the screening frequency for OLP should be increased.

4.6. Leukoplakia

Globally, leukoplakia is the most common OPMD in the world, with a prevalence of approximately 1%.[14] A systemic review indicated that the overall global malignant transformation rate of leukoplakia is 3.5%.[6] In Taiwan, leukoplakia is the most frequently occurring OPMD, which has the lowest rate of malignant transformation (1.68% in 5 years) in our study, which are compatible with those of the largest Indian study (0.3%–2.19%).[10] The annual malignant transformation rate in our study was 4.23 per 1000 person-years, which is lower than that in an Indian study (6.3 per 10,000 person-years).[17] A British study reported that the annual malignant transformation rate is 13.6 per 10,000 person-years,[10] and a systemic review indicated that the annual malignant transformation rate ranges from 20 to 30 per 10,000 person-years.[14]

Leukoplakia had the lowest malignant transformation rate in this study, which may be linked with our study design. Every patient received only 1 OPMD diagnosis code in the oral screening database. If a patient is diagnosed with 2 types of OPMDs, the clinical doctor tends to code the more severe one. Because leukoplakia often occurs together with other types of OPMDs, true leukoplakia prevalence might have been underestimated in our study. According to a previous study, pure leukoplakia cases had very low malignant transformation risk. However, since leukoplakia often appears together with other OPMDs, such combination do significantly increase the risk of malignant transformation.[18]

4.7. Erythroplakia

Erythroplakia is the least occurring OPMD in Western countries; thus, reports on erythroplakia are limited. The prevalence rate of erythroplakia is only available in Southeast Asia, and it is approximately 0.02%.[14] However, erythroplakia has a very high malignant transformation potential. A Sweden report demonstrated that mild dysplasia and moderate dysplasia was observed in 40% and 9% of erythroplakia lesions in the first biopsy respectively.[6] A research in Netherlands reported that more than 90% erythroplakia patients already exhibited oral carcinoma in the first biopsy (51% showed invasive carcinoma and 40% carcinoma in situ).[14] Our study, which may be a pilot study of erythroplakia in Asia, reported a transformation rate of 3.91% in 5 years and an annual malignant transformation of 9.75 per 1000 person-years.

4.8. Disease-free interval

In our study, among all OPMDs, the mean malignant transformation time for OLP was the shortest (8.07 months) (Fig. 4), which is compatible with 2 other previous results.[1,11] The annual malignant transformation incidence of other OPMDs is constant over time.[12]

4.9. Overall

The overall OPMD transformation rate was 4.32% (mean duration of transformation: 33.56 months; range: 6–67 months) in a previous Taiwan study[1] and 2.68% in our 5-year study. A British report indicated that the overall OPMD transformation rate was 2.6% on average in 12 years.[15] In this study, the average annual transformation rate of all OPMDs was 6.73 per 1000 person-years, which was higher than that of the comparison cohort (0.6 per 1000 person-years). The rate in the comparison cohort group is only compatible with that in a previous study in Taiwan, which estimated a 10-year transformation rate to be 0.0689 through Kaplan–Meier analysis.[1] In addition, the crude HR of malignant transformation was 11.20 times higher in the OPMD group when compared with the comparison cohort. After adjustment, the HR of malignant transformation rate was still 8.19 times higher in the OPMD group than that in the comparison cohort. Our data suggested that anyone diagnosed with OPMDs should be closely followed up.

Policy makers should consider assigning registered nurses to track patients with OLP after their first diagnosis and as well as all patients with OVH. The present finding may facilitate the development of follow-up measures and optimization of treatment strategies for dentists, otolaryngologists, and policy makers, thus reducing malignant transformation.

4.10. Risk factor

4.10.1. Age. Our study reported that in OPMDs and comparison cohort groups, differences were observed between age groups. In a previous Taiwan study, patients older than 45 years at the time of their first diagnosis showed a significant higher malignant potential than patients younger than 45 years ($P = .03$).[1] Some studies have demonstrated that patients older than 45 years of age experience early malignant transformation,[19] and a study reports that patients older than 70 years are at an extremely high risk of malignant transformation.[20]

4.10.2. Habits. In our study, betel nut chewing and smoking increased the malignant transformation risk to similar degrees in OPMD group (8.18; 7.89, after adjustment). In a previous Taiwanese study, smoking increased the oral cancer risk to 2.38 after adjustment for age and sex, whereas betel nut chewing increased the oral cancer risk to 4.59.[21] Heavy betel nut chewing increased the risk of leukoplakia to 32 times, whereas light use increased the risk to 16 times. Heavy smoking increased the risk of leukoplakia to 5 times, whereas light smoking increased the risk to 3.68 times.

4.10.3. Sex. In our study, female patients with OPMDs had an extremely high risk of malignant transformation (HR with the comparison cohort, female:male ratio: 21.14:7.94) (Table 3). Although the prevalence of OPMDs among women is low, once a woman is diagnosed with OPMDs, she should be closely followed up. In a Netherland study, female OPMD patients had a higher transformation risk than male patients.[10] However, another UK study reported that male OPMD patients had a higher risk than female patients.[20] There exists very few information on female OPMD patients so far due to the lack of cases. Our analysis revealed that even though female OPMD patients were rare, they did have a high malignant transformation rate. Female patients with OPMD require special attention from dentists and otolaryngologists.

5. Conclusion

This research might be the first nationwide study to evaluate the malignant transformation of OPMDs. According to our study results, the malignant transformation rates from the highest to the lowest were as follows: OVH > OSF > erythroplakia > OLP > leukoplakia. Habits of betel nut chewing and smoking both increased the malignant transformation risk to similar degree in OPMD group.

Our study also demonstrated that female patients diagnosed with OPMDs had an extremely higher risk of malignant transformation than male patients. Although the prevalence of OPMDs among women is low, once a woman is diagnosed with OPMDs, she should be closely followed up. Monitoring the condition of OPMDs is a crucial step in the prevention of invasive cancer formation.

5.1. Limitation of NHI database

Only 5 death codes are recorded in the death database, so if an autopsy has 5 more important findings than oral cancer, then oral cancer would not be recorded in the death database. Therefore, the true malignant transformation rate may be underestimated. However, the possibility of underestimation is low.

5.2. Limitation of oral screening data

Because the Taiwanese government only people with smoking and betel nut chewing habits, people with no aforementioned habits would not meet the criteria for this oral screening program covered by the government. According to a previous study, more than half of OLP patients had no history of tobacco or alcohol use,[16] so the total number of OLP cases may be underestimated by our oral screening database. Also, the oral mucosal screening database do not record alcohol drinking habit, which has been proven to be a risk factor for oral tumor formation.[10,20]

Patients with no smoking or betel nut chewing habit would not be involved in our study. The comparison cohort in our study comprised of individuals with either smoking or betel nut chewing habit.

There also existed a limitation of lacking grading for dysplasia. High-grade dysplasia may be significantly associated with cancer development.

5.3. Future goal

Oral screening data after 2014 are not available yet. Moreover, cancer registration data after 2016 are not available yet. Therefore, we may perform further study after the government releases these data.

Systemic disease, such as HCV infection,[11,16,22] immunological factors, using immunosuppression medication,[23,24] or heavy metals exposures[12] are possible risk factors for the malignant transformation. We will perform further survey by linking NHI oral mucosal screening databases with NHI systemic databases, to analyze the relation of systemic factors and malignant formation of OPMDs.

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