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Malignant transformation of oral potentially malignant disorders in Taiwanese indigenous peoples
A nationwide retrospective cohort study

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Abstract

Malignant transformation of oral potentially malignant disorders (OPMDs) is a potential cause of oral cancer. Currently, there is no research investigating the rate of malignant transformation of OPMDs into oral cancer in indigenous Taiwanese peoples. This study aimed to retrospectively investigate whether ethnicity (indigenous vs non-indigenous people) plays a role in increasing the malignant transformation rate of OPMDs into oral cancer. This study used data from the oral mucosal screening database and the Cancer Registry File, both of which originated from the National Health Insurance Research Database. We matched the baseline characteristics to control for confounding factors between indigenous peoples and non-indigenous peoples (17,768 indigenous subjects vs 71,072 non-indigenous subjects; 1:4 match) and compared the 2 cohorts. After matching for confounding factors such as age, sex, habits, and OPMD subtype, the malignant transformation rate was not statistically higher for indigenous people than for non-indigenous people. We also discovered that indigenous people with oral verrucous hyperplasia might have a higher chance of malignant transformation into oral cancer than the non-indigenous cohort. We conclude that ethnicity is not a risk factor for the malignant transformation of OPMDs into oral cancer; however, indigenous people with oral verrucous hyperplasia need to pay special attention and are suggested to undergo regular follow-ups for the occurrence of oral cancer.

Abbreviations: CRB = community review board, ICD = international classification of diseases, IRB = institutional review board, OLP = oral lichen planus, OPMD(s) = oral potentially malignant disorder(s), OSF = oral submucosal fibrosis, OVH = oral verrucous hyperplasia, SCC = squamous cell carcinoma, TMT = time to malignant transformation, VC = verrucous carcinoma.

Keywords: database, early detection of cancer, indigenous peoples, mouth neoplasms, Taiwan

1. Introduction

Oral cancer is the fifth leading cause of cancer-related death in Taiwan.[1] Oral potentially malignant disorders (OPMDs) are oral lesions with potential to develop into oral cancer (which is known as malignant transformation). According to the World Health Organization, OPMDs include leukoplakia, erythroplakia, oral submucosal fibrosis (OSF), oral verrucous hyperplasia (OVH), and oral lichen planus (OLP). According to previous studies, the process of malignant transformation takes time and is related to patient age, sex, lifestyle, and ethnicity.[2,3] The population of Taiwan is approximately 24 million and comprises different ethnic groups, including Hokkien (73%), mainland Chinese (13%), Hakka (12%), and Taiwanese indigenous peoples (2%).[4] The Taiwanese indigenous peoples comprise 16 indigenous communities, with a population of approximately 53,000, accounting for 2.3% of the total population. They have been perceived by society as habituating to betel nut chewing, smoking, and drinking. To lower the oral cancer prevalence in Taiwan, the government launched a free oral mucosal screening program in 2010 and has been screening people with a history of betel nut chewing or smoking to detect OPMDs and oral

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cancer at an early stage. Compulsory treatment for oral cancer and close follow-up for OPMDs patients were also included in the program.

Currently, there are no epidemiological surveys of the malignant transformation of OPMDs to oral cancers, especially among different ethnic groups in Taiwan. Our goal was to investigate the rate of malignant transformation of OPMDs into oral cancer based on ethnicity (Taiwanese indigenous people vs non-indigenous people) to determine whether the incidence of oral cancer is related to habits or ethnicity. We need to identify risk factors and high-risk groups so that the government can improve the screening program and tailor it to individual needs. To conduct this study, we used data from the oral mucosal screening database and matched the data between indigenous people and non-indigenous people to control for confounding factors and to determine whether ethnicity plays a role in the malignant transformation rate of oral cancer. This research can assist policymakers in establishing public policies that are in line with the Taiwan Precision Medicine Initiative and improve the practice of precision medicine among different ethnic groups in Taiwan.

2. Materials and methods

2.1. Data source

Taiwan launched a single-payer National Health Insurance program on March 1st, 1995.[5,6] The enrollment rate of this health insurance program was 97% of the population of 22.96 million legal Taiwanese residents at the end of 1995, reached 99% in 1997 and 99.9% in 2014, and has maintained a higher coverage level since then.[5,6] This Health Insurance program records medical information, including diagnostic and management codes and basic patient information in the Registry of Beneficiaries File in their Health Insurance research database, and provides de-identified and encrypted patient data for qualified researchers. In Taiwan, every hospital/clinic has a coder team to ensure the accuracy of the diagnostic and management codes. Taiwan's National Health Insurance Bureau is responsible for auditing medical payments through a comprehensive review of medical records. The cancer registry database, which also belongs to the National Health Insurance Research Database, contains detailed cancer information, such as the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10 codes for diagnoses, date of diagnosis, whether surgery was performed, and the follow-up of cancer status since 2002.

The Taiwanese government has started oral mucosal screening since 2010 for people who are over 30 years old with a history of smoking or betel nut chewing, even if the individual had quit those habits, and for indigenous people who are over 18 years old, to improve oral cancer detection at an early stage. Dentists and otolaryngologists performed free oral mucosal screening and recorded the clinical data of the patients in the oral mucosal screening database, which also belongs to the National Health Insurance Research Database. The oral screening database contains clinical diagnosis, biopsy results, follow-up, further treatment conditions, smoking or betel nut chewing history, place of residence, household register, and detailed information of the screen and clinic/hospital, whether the screener is an indigenous person or not. Clinical diagnoses included oral mucosal erosion, oral ulcers, oral canker sores, leukoplakia, erythroplakia, oral submucosal fibrosis, oral verrucous hyperplasia, oral lichen planus, and highly suspected malignancy.

We collected data from the oral mucosal screening database and the cancer registry database, both of which originated from the National Health Insurance Research Database; therefore, all identifiable personal data were de-identified and encrypted. The records of the oral mucosal screening database contain the

following information, which was valuable for achieving our study goal:

A. The basic information of the person being screened, including a tick box marked by the screener himself or herself to indicate whether he or she is an indigenous person.
B. Whether there is a history of betel nut chewing or cigarette smoking.
C. The results of oral mucosal screening included OPMDs, oral cancer, high suspicion of oral cancer, oral mucosal erosion, oral ulcer, or no abnormality detected.

Since the indigenous peoples' identification records in the Registry of Beneficiaries File for the National Health Insurance are reviewed and confirmed by the government, the indigenous cohort in this research included only those that have been registered as indigenous peoples in both the Registry of Beneficiaries File and the oral mucosal screening database. For the non-indigenous cohort, this research included only those that have been registered as non-indigenous peoples in both the Registry of Beneficiaries File and the oral mucosal screening database. If the screener neither ticked the indigenous box nor the non-indigenous box in the oral mucosal screening database in the basic information of oral mucosal screening data, this person was excluded from this study.

The database is located in the Southern Taiwan Health and Welfare Data Science Center, where the original data cannot be obtained for patient privacy, and the researchers can only obtain the results of the statistical analyses. The principal investigator of this research is qualified to process the data and because all identifiable personal data have been encrypted, the malignant transformation analysis of our study was granted an exemption from a full ethical review by the Institutional Review Board of Chi Mei Medical Center (IRB Serial No.:10705-E05, Supplementary File 1, http://links.lww.com/MD/H973). The Institutional Review Board of Chi Mei Medical Center approved the research on indigenous people (IRB Serial No.:10810-002, Supplementary File 2, http://links.lww.com/MD/H974). We have also obtained the qualifications and approval from the Taiwan Indigenous Community Review Board (CRB) (https://crb.cip.gov.tw/) of the Council of Indigenous Peoples (CRB Serial No.: CRB-108-059, Supplementary File 3, http://links.lww.com/MD/H975) on the part of research related to indigenous peoples.

2.2. Linking the data files

Patients highly suspected of having malignancy or those whose diagnosis could not be determined by a clinician were referred to the hospital to have oral biopsies for histological confirmation. If the histological report confirmed the lesions as squamous cell carcinoma (SCC), verrucous carcinoma (VC), or carcinoma in situ, the patient was immediately referred to a hospital for cancer treatment, and the patient's data were recorded in the cancer registry database. In our study, we excluded patients who had a history of oral cancer before the diagnosis date of OPMD based on the cancer registry database. The ICD-9-CM and ICD-10 codes of oral cancer were used for data collection from the cancer registry database.

We linked the following 3 files with the 2010-2013 oral mucosal screening file: the Cancer Registry Database (Cancer Registry File, Long File Edition [LF 2007–2015]); Cause of Death Data (2007–2016); and Multiple Causes of Death Data (2008–2016) which provided the major and minor causes of death of the subjects, and autopsy records that showed whether the subjects had undiagnosed oral cancers. Linking these data files allowed us to investigate the rate of malignant transformation of OPMDs into oral cancer. If a patient underwent oral screening more than once between 2010 and 2013, we only included his first OPMD diagnosis record in our study.

2.3. Patient selection

Figure 1 presents the flow chart of this study. The subjects were selected from the oral mucosal screening database. We reviewed the data in the oral mucosal screening database from 2010 to 2013 and linked these subjects with the cancer registry database to investigate whether OPMD patients subsequently developed oral cancer before 2016. Patients with high suspicion of oral cancer in the screening results were excluded from our study. Based on ethnicity records, subjects classified as indigenous were placed in the experimental group, while the non-indigenous subjects were placed under the control group. There was a 1:4 match between the indigenous and non-indigenous cohorts by age, OPMD subtype, and betel nut chewing history, which is considered the most important factor for the malignant transformation of OPMDs.[7]

2.4. Statistical analysis

The baseline information of subjects was presented as frequencies expressed as percentages, and Pearson's chi-square test was used to compare the differences between the indigenous and non-indigenous cohorts. The time to malignant transformation (TMT) (in years, from OPMD to oral cancer) and the follow-up period (in years) from each cohort were expressed as medians with interquartile ranges and compared (indigenous vs non-indigenous) using the Wilcoxon rank-sum test. The relative risks of malignant transformation between the indigenous and non-indigenous cohorts expressed as hazard ratios (95% CI) were estimated using Cox proportional hazard regression after adjusting for the potential risk factors for oral cancer. The difference in the cumulative incidence of malignant transformation between the 2 cohorts was calculated using the log-rank test. For the OPMD subtypes, we investigated whether there would be any difference in the cumulative malignant transformation rate. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). The trend in the cumulative incidence rate was plotted using SPSS version 21 (SPSS Inc., Chicago, IL). The P value was set at .05.

3. Results

The 1:4 matching process resulted in the inclusion of 17,768 and 71,072 subjects in indigenous and non-indigenous cohorts, respectively. Table 1 presents a summary of the demographic data for both cohorts. The matching was based on the OPMD subtype (except for oral lichen planus due to the low number of cases), age, sex, and betel nut chewing status, based on previous observational studies.[7] The right side of Table 1, labeled as the "matched non-indigenous control group," demonstrates the result of successful matching by age, betel nut chewing status, and OPMD subtype. Table 1 also demonstrates that the indigenous cohort had a significantly lower rate of malignant transformation than the matched non-indigenous control group (0.25 vs 0.38, P = .0097). There was no significant difference in TMT between the 2 cohorts. The follow-up period was significantly longer in the indigenous cohort than in the non-indigenous cohort (3.92 years vs 3.59 years, P < .001).

Table 2 shows the hazard ratios of the potential risk factors for the malignant transformation of OPMDs. After matching, we determined the hazard ratio between the indigenous and non-indigenous cohorts to determine whether ethnicity affected the malignant transformation rate. The hazard ratio of indigenous people developing malignant transformation compared to the matched non-indigenous control group was 0.77, which was not statistically significant. However, the malignant transformation rate was positively associated with betel nut chewing, age, sex, and the OPMD subtype. All OPMDs had a significantly higher probability for malignant transformation when compared with the non-OPMD (normal screening result) group, whether they were adjusted by age, gender, betel nut chewing status, and smoking status.

Figure 2 shows the cumulative incidence of malignant transformation. The figure shows that those with OPMDs had a higher probability of malignant transformation than those without OPMDs, regardless of ethnicity. The figure also reveals that the indigenous cohort had a lower probability of malignant transformation than the matched non-indigenous control group regardless of the OPMDs status (the blue and green lines are
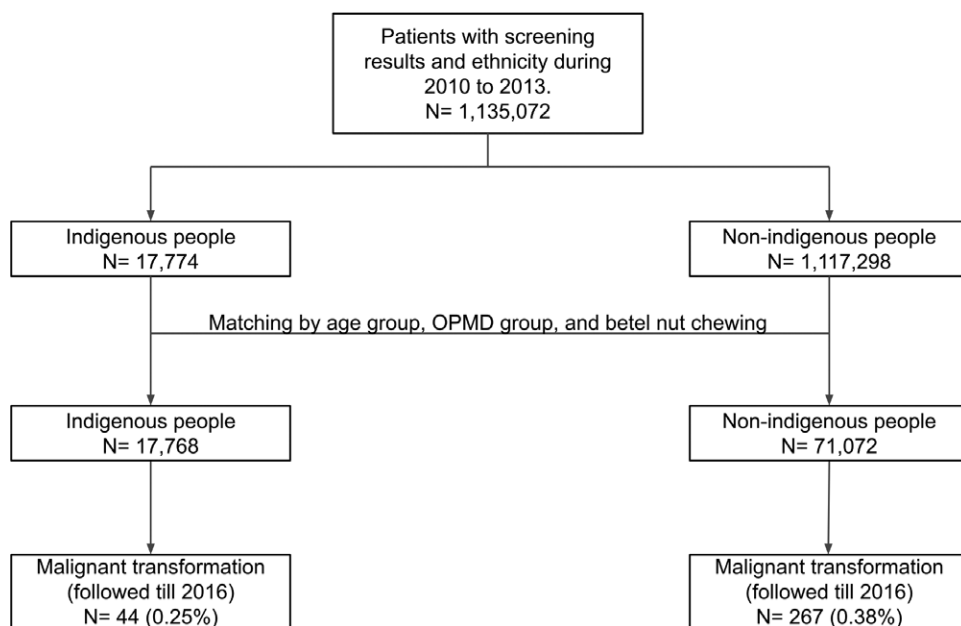
Figure 1. Flowchart of the study detailing the methods of patient selection and inclusion. The 1:4 matching process of Taiwanese indigenous peoples and non-indigenous cohort, by OPMD subtype, age, gender, and betel nut chewing status, was based on previous observational studies.[7] OPMD = oral potentially malignant disorders.

Table 1

Demographic data of the indigenous people and non-indigenous control group, before and after matching.

	Non-match			Matched		
	Indigenous people	Non- indigenous control group	P value	Indigenous people	Non- indigenous control group	P value
Age group			<.0001*			>.9999
<40	3695(20.79)	310128(27.76)		3693(20.78)	14772(20.78)	
40–60	8846(49.77)	534140(47.81)		8846(49.79)	35384(49.79)	
60≧	5233(29.44)	273030(24.44)		5229(29.43)	20916(29.43)	
Gender			<.0001*			<.0001*
Male	9827(55.29)	887936(79.47)		9821(55.27)	57909(81.48)	
Female	7947(44.71)	229362(20.53)		7947(44.73)	13163(18.52)	
Betel nut chewing, yes	14296(80.43)	590084(52.81)	<.0001*	14292(80.44)	57168(80.44)	>.9999
Smoking, yes	11853(66.69)	1005886(90.03)	<.0001*	11850(66.69)	62360(87.74)	<.0001*
OPMD subtypes			<.0001*			>.9999
Normal group	17019(95.75)	1062933(95.13)		17019(95.78)	68076(95.78)	
Leukoplakia	491(2.76)	38359(3.43)		491(2.76)	1964(2.76)	
Erythroplakia	125(0.70)	5216(0.47)		125(0.70)	500(0.70)	
Oral verrucous hyperplasia	34(0.19)	1605(0.14)		34(0.19)	136(0.19)	
Oral submucosal fibrosis	99(0.56)	8515(0.76)		99(0.56)	396(0.56)	
Oral lichen planus	6(0.03)	670(0.06)		-	-	
Oral cancer	44(0.25)	3694(0.33)	.0551	44(0.25)	267(0.38)	.0097*
TMT, in years			.1711			.2981
Median (Q1–Q3)	2.68(1.18–3.66)	2.18(1.01–3.35)		2.68(1.18–3.66)	2.21(1.14–3.44)	
Mortality	652(3.67)	29096(2.60)	<.0001*	651(3.66)	2125(2.99)	<.0001*
Follow-up period, in years			<.0001*			<.0001*
Median (Q1–Q3)	3.92(2.74–5.24)	3.56(2.45–4.69)		3.92(2.74–5.24)	3.59(2.46–4.71)	

We matched the non-indigenous cohort to the indigenous cohort by OPMD subtype, age, sex, and betel nut chewing status, based on previous observational studies.[7]

OPMD = oral potentially malignant disorder, TMT = time to malignant transformation.

*P value was set at .05, calculated using Pearson's chi-square test.

Table 2

Hazard ratios of the risk factors for malignant transformation of OPMDs in the indigenous cohort and matched non-indigenous control group.

	Crude HR (95% C.I.)	P value	Adjusted HR† (95% C.I.)	P value
Ethnic group				
Indigenous peoples	0.59(0.43–0.81)	.0012*	0.77(0.56–1.08)	.1263
Matched non-indigenous peoples	Ref		Ref	
Age group				
<40	Ref.		Ref.	
40–60	2.41(1.65–3.52)	<.0001*	2.49(1.71–3.64)	<.0001*
60≧	1.79(1.19–2.71)	.0054*	2.11(1.40–3.19)	.0004*
Gender				
Male	3.62(2.37–5.54)	<.0001*	2.75(1.75–4.31)	<.0001*
Female	Ref.		Ref.	
Betel nut chewing, yes	2.26(1.55–3.29)	<.0001*	1.75(1.20–2.55)	.0037*
Smoking, yes	1.66(1.16–2.37)	.0052*	1.06(0.73–1.55)	.7537
OPMD subtypes				
Normal group	Ref.		Ref.	
Leukoplakia	6.66(4.82–9.20)	<.0001*	5.91(4.27–8.19)	<.0001*
Erythroplakia	10.60(6.63–16.93)	<.0001*	9.38(5.88–14.97)	<.0001*
Oral verrucous hyperplasia	23.20(12.66–42.50)	<.0001*	20.57(11.32–37.38)	<.0001*
Oral submucosal fibrosis	10.26(5.98–17.61)	<.0001*	9.62(5.62–16.47)	<.0001*

OPMD = oral potentially malignant disorders.

†Adjusted by age, sex, betel nut chewing status, smoking status, and OPMD subtype based on previous observational studies.[7]

*P value was set at .05, calculated using Pearson's chi-square test.

both lower than the other 2 lines that represent the matched non-indigenous control group).

We reviewed the data from the oral mucosal screening database from 2010 to 2013 and these subjects developed oral cancer before 2016.

Table 3 presents the risk of malignant transformation of each OPMD subtype for the indigenous cohort compared to the matched non-indigenous control group (as the reference). The table shows that Indigenous people with OVH had a higher possibility of malignant transformation than the matched non-indigenous control group, but the difference was not statistically

significant. For other OPMDs, the hazard ratios in the indigenous cohort were lower than those in the matched non-indigenous control group, although the differences were not statistically significant.

4. Discussion

Lifestyle habits and genetic predispositions unique to ethnic groups are considered key factors in cancer formation.[4,8] Previous studies have shown that certain genes can increase the malignant transformation rate of oral cancer. For example,
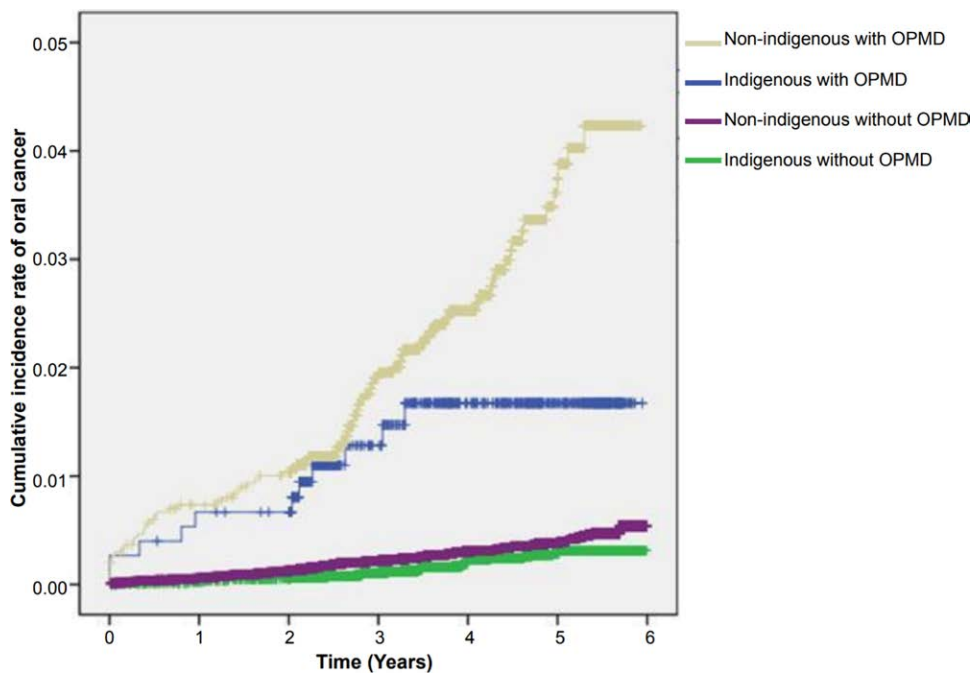
Figure 2. The K-M plot of malignant transformation of the indigenous cohort and matched non-indigenous control group, with or without OPMDs. OPMD: oral potentially malignant disorders. Indigenous: indigenous peoples. Non-indigenous: matched non-indigenous control group. The 1:4 matching process of Taiwanese indigenous peoples and non-indigenous cohort, by OPMD subtype, age, gender, and betel nut chewing status, was based on previous observational studies.[7] We reviewed the data from the oral mucosal screening database from 2010 to 2013 and these subjects developed oral cancer before 2016.

Table 3

Hazard ratios of OPMD subtypes for malignant transformation among indigenous cohort, compared with the matched non-indigenous control group (as reference).

OPMD subtypes	Crude HR (95% C.I.)	P value	Adjusted HR† (95% C.I.)	P value
Normal group				
Indigenous	0.62(0.43–0.90)	.0120	0.81(0.55–1.19)	.2820
Matched non-indigenous	reference		reference	
Leukoplakia				
Indigenous	0.58(0.25–1.38)	.2190	0.91(0.39–2.10)	.8190
Matched non-indigenous	reference		reference	
Erythroplakia				
Indigenous	0.20(0.03–1.47)	.1122	0.28(0.05–1.61)	.1537
Matched non-indigenous	reference		reference	
Oral verrucous hyperplasia				
Indigenous	1.43(0.38–5.37)	.6012	1.77(0.44–7.06)	.4213
Matched non-indigenous	reference		reference	
Oral submucosal fibrosis				
Indigenous	0.30(0.04–2.32)	.251	0.71(0.13–4.04)	.7006
Matched non-indigenous	reference		reference	

OPMD = oral potentially malignant disorder.

†Adjusted by age, sex, betel nut chewing status, and smoking status based on previous observational studies.[7]

*P value was set at .05, calculated using Pearson's chi-square test.

the gene expression of glutathione S-transferase and N-acetyl transferase could be determinants of oral carcinoma. Mutations in *p53*, *cytochrome P450*, and *RAS* genes are strongly associated with dysplasia formation.[9] Genetic polymorphisms can result in resistance or susceptibility to oral carcinoma in different ethnic groups.[4] A recent study also showed that genetic testing can be used to identify high-risk groups for OPMDs that may develop into oral cancer.[10–12] Some studies have also suggested that exposure to heavy metals, such as environmental nickel, may be associated with an increased risk of malignant transformation of OPMDs.[13–15] Arsenic and chromium in farm soils have been identified as new risk factors for oral cancer development.[15,16] A study demonstrated that the trace element status is significantly different among different ethnic groups, as demonstrated by hair Ca, Mn, and Se, after adjusting for confounders.[17] However, further research is required to determine whether special habits related to local culture play a crucial role in the occurrence of oral cancer.[18] Certain immunological factors, infections involving human papillomavirus, *Candida albicans,* hepatitis C virus, and immunosuppressive medications such as topical corticosteroids for treating local OLP lesions, have been identified as possible risk factors for the malignant transformation of OPMDs.[19–22] One explanation for these findings is that inflammatory infiltrates cause oxidative stress, which leads to the release of inflammatory cytokines that activate transcription factors in the premalignant cells.

4.1. Potential risk factors

4.1.1. Age. According to previous studies, age plays an important role in the malignant transformation of OPMDs. In a previous Taiwanese study, older screeners, when first diagnosed with OPMDs, showed a significant higher malignant potential than that of younger screener.[1] OPMD patients older than 45 years old also experience earlier malignant transformation than younger ones.[23] Patients with advanced age, such as older than 60 years old[7] and/or 70 years old,[24] may be more susceptible to develop malignant transformation.

4.1.2. Gender. In previous studies, the prevalence of OPMDs among women is low, and male gender can be viewed as an independent risk factor of the malignant transformation of OPMDs into oral cancer.[24] Moreover, a Taiwanese indigenous study reported that gender differences correlate with oral cancer survival rate.[4]

4.1.3. Betel nut chewing habit. In previous Taiwanese studies, betel nuts chewing can increase the oral cancer risk to several times, before and after adjustment for age and gender.[7,25] An elimination of betel nuts consumption may prevent 26% of malignant transformation to oral cancer in the OPMDs population.[25]

Our research focused on the association between ethnicity and the malignant transformation rate of OPMD by comparing the indigenous and non-indigenous cohorts. Based on the information from the above-mentioned publications, we matched these 3 factors: age, gender, and betel nut chewing habit for the potential effects they may have on oral malignant transformation. After matching, we found that the malignant transformation rate was not higher for indigenous peoples; on the contrary, it was even lower. Our research also discovered that only indigenous people with OVH have a higher chance of malignant transformation into oral cancer than non-indigenous people. OVH and VC are very different clinicopathologically.[26] OVH can turn into VC or SCC[27]; while VC can turn from OVH or other OPMDs.[27]

After matching for baseline characteristics, indigenous people did not have a statistically different malignant transformation potential compared to the non-indigenous cohort. Therefore, we conclude that ethnicity (indigenous group vs non-indigenous group) is not a risk factor for the malignant transformation of OPMDs to oral cancer; however, indigenous people with OVH need to pay special attention and should undergo regular follow-up checkups for the occurrence of oral cancer. Betel nut chewing and alcohol overconsumption, which are common practices in indigenous populations, are known high-risk factors for the malignant transformation of OPMDs to oral cancer[28]; thus, providing free oral mucosal screening for indigenous peoples who are over 18 years old is a useful policy to lower the prevalence of oral cancer.

The higher malignant transformation rate of OVH among indigenous people may be due to the following factors; however, more studies are required to determine the relationship between each risk factor and the malignant transformation of OVH. We are currently conducting a series of follow-up studies, and we will soon make the results public.

A. Betel nut chewing. In a previous study in Taiwan, heavy use of betel nut was highly associated with dysplasia and malignant transformation of OVH.[29] Our study showed a higher rate of betel nut use among indigenous people than among non-indigenous people (80.43 vs 52.81%; $P < .001$).

B. Genes that regulate carcinomatosis among different ethnicities.[29]

C. Alcohol consumption. Alcohol consumption has been associated with VC formation of VC. Indigenous people tend to drink more as a cultural custom, which could contribute to the rate of malignant transformation of OMPDs.[30,31]

5. Conclusion

We conclude that ethnicity is not an independent risk factor for the malignant transformation of OPMDs. This study also shows that the practice of betel nut chewing is more common among indigenous peoples and that both smoking and betel nut chewing have been previously identified as risk factors for oral cancer. The current government policy that provides free oral mucosal screening, which starts at a young age in indigenous peoples, is a reasonable practice. Indigenous individuals with OVH should receive more frequent follow-up screenings, which can be included in the current government policy.

5.1. The limitations of this study

This study used data from oral mucosal screening database, originated from the National Health Insurance Research Database. The oral mucosal screening database does not record the different grades of atypical cell morphology.

Alcohol consumption has been linked to oral cancer formation and is highly prevalent among Taiwanese individuals (5.6%–8.3%).[32] Heavy drinkers exhibit an 8-fold higher risk of developing leukoplakia,[25] a rapid malignant transformation of OPMDs, and a late stage of oral cancer at the time of the first diagnosis.[24,33] However, the oral screening database did not have a record of the amount or duration of alcohol consumption. Further research is required to evaluate the correlation between malignant transformation and drinking habits.

Betel nut usage has also been linked to the malignant transformation of OVH.[29] Our future research will address whether there is a correlation between light, moderate, and heavy betel nut usage and the development of oral cancer or malignant transformation of OPMDs.

Further investigation into the long-term follow up of malignant transformation is needed. However, this research is the only currently existed large 6-year research studying the malignant transformation of OPMDs into oral cancers from a nationwide database. As the first follow-up study, the preset study can provide researchers the possible reference for further investigation.

Author contributions

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Supervision: Ying-Jen Chang.
Validation: Chung-Han Ho.
Visualization: I-An Chen.
Writing – original draft: Kuo-Chuan Hung.
Writing – review & editing: I-An Chen.

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