Observational Study

Medicine

OPEN

Malignant transformation of oral potentially malignant disorders in Taiwanese indigenous peoples

A nationwide retrospective cohort study

I-An Chen, MD[a], Sheng-Fu Chiu, DDS[b], Kuo-Chuan Hung, MD[a,c], Chia-Hung Yu, MD[a], Yi-Chen Chen, MS[d], Chung-Han Ho, PhD[d,e], Wei-Fan Chiang, DDS[b,f], Ying-Jen Chang, MD[a,g,*]

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

This work was supported by the Ministry of Science and Technology, Taiwan [grant no. MOST 108-2321-B-006-010, and MOST 107-2321-B-006-007] and by Chi Mei Medical Center, Liouying [grant no. CLFHR10824].

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Department of Anesthesiology, Chi Mei Medical Center, Tainan City, Taiwan, [b] Department of Oral and Maxillofacial Surgery, Chi Mei Medical Center, Liouying, Tainan City, Taiwan, [c] Department of Hospital and Health Care Administration, College of Recreation and Health Management, Chia Nan University of Pharmacy and Science, Tainan City, Taiwan, [d] Department of Medical Research, Chi Mei Medical Center, Tainan City, Taiwan, [e] Department of Information Management, Southern Taiwan University of Science and Technology, Tainan City, Taiwan, [f] School of Dentistry, National Yang-Ming University, Taipei City, Taiwan, [g] Department of Recreation and Health-Care Management, College of Recreation and Health Management, Chia Nan University of Pharmacy and Science, Tainan City, Taiwan.

**Correspondence: Ying-Jen Chang, Department of Anesthesiology, Chi Mei Medical Center, No.901, Zhonghua Rd., Yongkang Dist., Tainan City 71004, Taiwan (e-mail: 0201day@yahoo.com.tw).*

How to cite this article: Chen I-A, Chiu S-F, Hung K-C, Yu C-H, Chen Y-C, Ho C-H, Chiang W-F, Chang Y-J. Malignant transformation of oral potentially malignant disorders in Taiwanese indigenous peoples: A nationwide retrospective cohort study. Medicine 2022;101:46(e31910).

Received: 16 September 2022 / Received in final form: 27 October 2022 / Accepted: 28 October 2022

http://dx.doi.org/10.1097/MD.0000000000031910

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

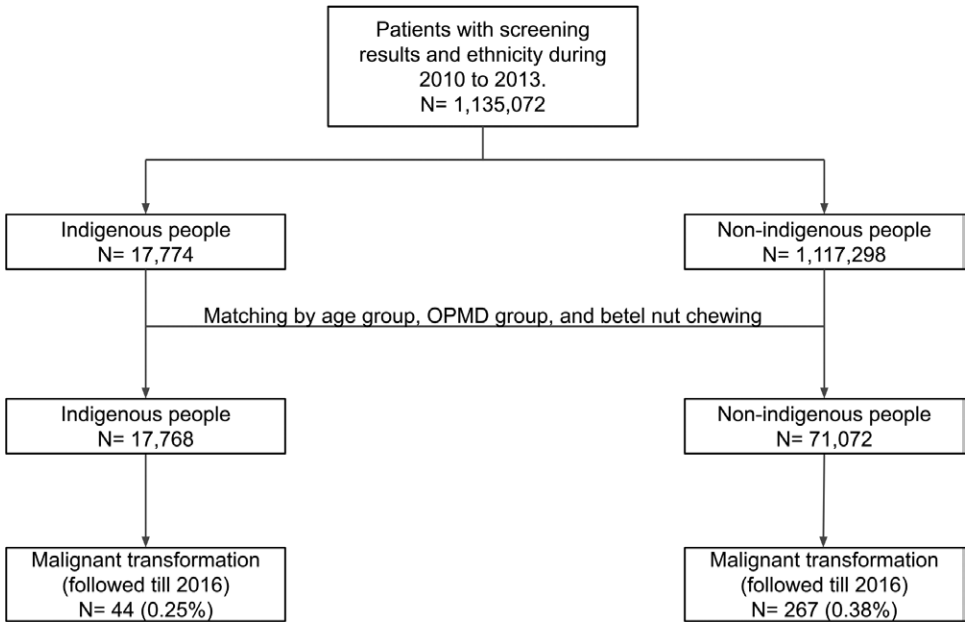

Figure 1. Flowchart of the study detailing the methods of patient selection and inclusion. The 1:4 matching process of Taiwanese indigenous peoples and non-indigenous cohort, by OPMD subtype, age, gender, and betel nut chewing status, was based on previous observational studies.[7] OPMD = oral potentially 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,

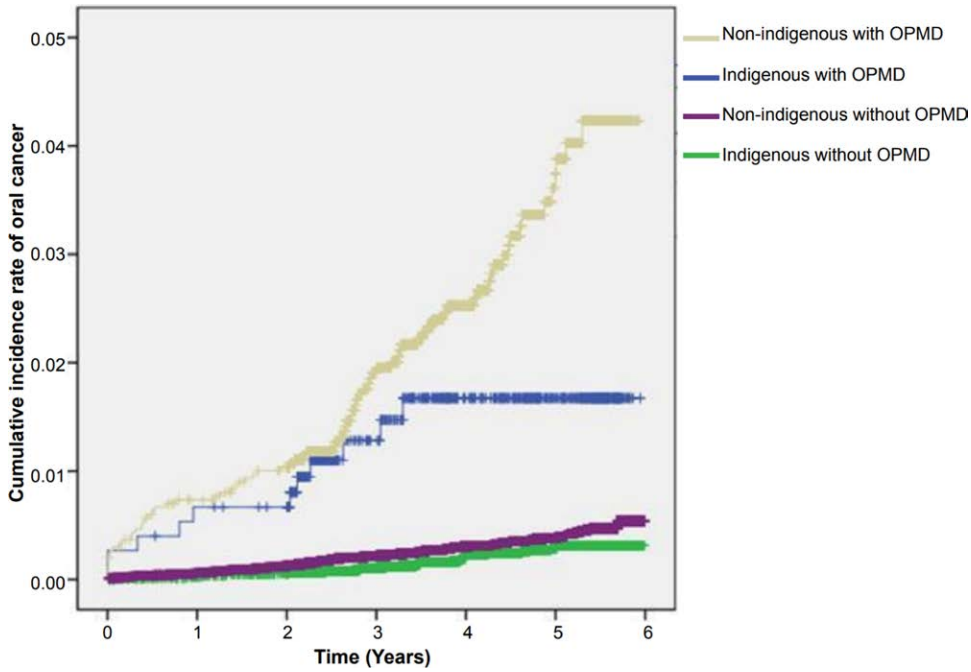

Figure 2. The K-M plot of malignant transformation of the indigenous cohort and matched non-indigenous control group, with or without OPMDs. OPMD: oral potentially malignant disorders. Indigenous: indigenous peoples. Non-indigenous: matched non-indigenous control group. The 1:4 matching process of Taiwanese 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.

Acknowledgments

We thank the Southern Taiwan Health and Welfare Data Science Center for providing the data and protecting patient privacy.

We thank the Taiwan Indigenous Community Review Board of the Council of Indigenous Peoples (CRB, [https://crb.cip.gov.tw/]) for providing us with educational training (Supplementary File 4: CRB Human Research Ethics Committee Education Course, http://links.lww.com/MD/H976), for allowing us to start this research, for reviewing and approving our research regarding the part related to the indigenous peoples, and for consenting to publish this research (Supplementary File 3: CRB Research Approval Certificate, http://links.lww.com/MD/H975, and Supplementary File 5: CRB Publication Permission Certificate, http://links.lww.com/MD/H977).

We thank Ms. Claire Chang (M.A., English Lecturer in the Department of Medicine at National Taiwan University, Taiwan) for providing language assistance, including improvements in grammar, sentence structure and general readability. We thank the Foreign Language Center of National Cheng Kung University (NCKU) for providing English editing services, which included grammar corrections and improvements in sentence structure and general readability (Supplementary File 6: NCKU English revision certificate, http://links.lww.com/MD/H978).

Author contributions

Conceptualization: Ying-Jen Chang.
Data curation: Sheng-Fu Chiu.
Formal analysis: Yi-Chen Chen, Chung-Han Ho.
Funding acquisition: Sheng-Fu Chiu, Wei-Fan Chiang.
Investigation: Yi-Chen Chen, Chung-Han Ho.
Methodology: Ying-Jen Chang.
Project administration: Chia-Hung Yu.
Resources: Sheng-Fu Chiu.
Software: Ying-Jen Chang.
Supervision: Ying-Jen Chang.
Validation: Chung-Han Ho.
Visualization: I-An Chen.
Writing – original draft: Kuo-Chuan Hung.
Writing – review & editing: I-An Chen.

References

[1] Wang YY, Tail YH, Wang WC, et al. Malignant transformation in 5071 southern Taiwanese patients with potentially malignant oral mucosal disorders. BMC Oral Health. 2014;14:99.
[2] Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. Int J Cancer. 2003;105:546–51.
[3] Higashiura Y, Kajihara H, Shigetomi H, et al. Identification of multiple pathways involved in the malignant transformation of endometriosis (Review). Oncol Lett 2012;4:3–9.
[4] Chen PH, Shieh TY, Ho PS, et al. Prognostic factors associated with the survival of oral and pharyngeal carcinoma in Taiwan. BMC Cancer. 2007;7:101.
[5] Chen L, Yip W, Chang MC, et al. The effects of Taiwan's National Health Insurance on access and health status of the elderly. Health Econ. 2007;16:223–42.
[6] Chang YJ, Ho CH, Chen JY, et al. Epidemiological profile and obstetric outcomes of patients with peripartum congestive heart failure in Taiwan: a retrospective nationwide study. BMC Pregnancy Childbirth. 2017;17:302.
[7] Chiu SF, Ho CH, Chen YC, et al. Malignant transformation of oral potentially malignant disorders in Taiwan: an observational nationwide population database study. Medicine (Baltim). 2021;100:e24934.
[8] Zhou H, Wu W, Wang F, et al. Tea consumption is associated with decreased risk of oral cancer: a comprehensive and dose-response meta-analysis based on 14 case-control studies (MOOSE compliant). Medicine (Baltim). 2018;97:e13611.
[9] Lin CY, Pan TS, Ting CC, et al. Cytochrome p450 metabolism of betel quid-derived compounds: implications for the development of prevention strategies for oral and pharyngeal cancers. ScientificWorldJ 2013;3:618032.
[10] Alaizari NA, Sperandio M, Odell EW, et al. Meta-analysis of the predictive value of DNA aneuploidy in malignant transformation of oral potentially malignant disorders. J Oral Pathol Med. 2018;47:97–103.
[11] Meng Y, Yang P, Ma L. Prognostic and clinical implications of c-erbB-2 expression in patients with oral cancer: a meta-analysis. Medicine (Baltim). 2020;99:e20575.
[12] Su CW, Huang YW, Chen MK, et al. Polymorphisms and plasma levels of tissue inhibitor of metalloproteinase-3: impact on genetic susceptibility and clinical outcome of oral cancer. Medicine (Baltim). 2015;94:e2092.
[13] Tsai KY, Su CC, Chiang CT, et al. Environmental heavy metal as a potential risk factor for the progression of oral potentially malignant disorders in central Taiwan. Cancer Epidemiol 2017;47:118–24.
[14] Yuan TH, Lian Ie B, Tsai KY, et al. Possible association between nickel and chromium and oral cancer: a case-control study in central Taiwan. Sci Total Environ. 2011;409:1046–52.
[15] Su CC, Lin YY, Chang TK, et al. Incidence of oral cancer in relation to nickel and arsenic concentrations in farm soils of patients' residential areas in Taiwan. BMC Public Health. 2010;10:67.
[16] Yang SY, Lin JM, Lin WY, et al. Cancer risk assessment for occupational exposure to chromium and nickel in welding fumes from pipeline construction, pressure container manufacturing, and shipyard building in Taiwan. J Occup Health. 2018;60:515–24.
[17] Skalny AV, Mona W, Kao R, et al. Hair trace element levels in han and indigenous hualien inhabitants in Taiwan. Biol Trace Elem Res. 2019;191:1–9.
[18] Cheng MT, Shih FY, Tsai CL, et al. Impact of major illnesses and geographic regions on do-not-resuscitate rate and its potential cost savings in Taiwan. PLoS One. 2019;14:e0222320.
[19] Irani S. Pre-cancerous lesions in the oral and maxillofacial region: a literature review with special focus on etiopathogenesis. Iran J Pathol 2016;11:303–22.
[20] Rapado-Gonzalez O, Martinez-Reglero C, Salgado-Barreira A, et al. Association of salivary human papillomavirus infection and oral and oropharyngeal cancer: a meta-analysis. J Clin Med. 2020;9:1305.
[21] Rutkoski H, Tay DL, Dixon BL, et al. A multi-state evaluation of oral health students' knowledge of human papillomavirus-related oropharyngeal cancer and HPV vaccination. J Cancer Educ. 2019;35:1017–25.
[22] Hsue SS, Wang WC, Chen CH, et al. Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders: a follow-up study based in a Taiwanese hospital. J Oral Pathol Med. 2007;36:25–9.
[23] Dost F, Le Cao K, Ford PJ, et al. Malignant transformation of oral epithelial dysplasia: a real-world evaluation of histopathologic grading. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:343–52.
[24] Goodson ML, Sloan P, Robinson CM, et al. Oral precursor lesions and malignant transformation--who, where, what, and when? Br J Oral Maxillofac Surg. 2015;53:831–5.
[25] Shiu MN, Chen TH, Chang SH, et al. Risk factors for leukoplakia and malignant transformation to oral carcinoma: a leukoplakia cohort in Taiwan. Br J Cancer. 2000;82:1871–4.
[26] Zhu LK, Ding YW, Liu W, et al. A clinicopathological study on verrucous hyperplasia and verrucous carcinoma of the oral mucosa. J Oral Pathol Med. 2012;41:131–5.
[27] Alkan A, Bulut E, Gunhan O, et al. Oral verrucous carcinoma: a study of 12 cases. Eur J Dent 2010;4:202–7.
[28] McCarter K, Baker AL, Wolfenden L, et al. Smoking and other health factors in patients with head and neck cancer. Cancer Epidemiol. 2022;79:102202.
[29] Wu MH, Luo JD, Wang WC, et al. Risk analysis of malignant potential of oral verrucous hyperplasia: a follow-up study of 269 patients and copy number variation analysis. Head Neck 2018;40:1046–56.
[30] Peng Q, Wang Y, Quan H, et al. Oral verrucous carcinoma: from multifactorial etiology to diverse treatment regimens (Review). Int J Oncol. 2016;49:59–73.
[31] Walvekar RR, Chaukar DA, Deshpande MS, et al. Verrucous carcinoma of the oral cavity: a clinical and pathological study of 101 cases. Oral Oncol. 2009;45:47–51.
[32] Tsao YC, Li WC, Yeh WC, et al. The association between metabolic syndrome and related factors among the community-dwelling indigenous population in Taiwan. Int J Environ Res Public Health. 2020;17:8958.
[33] Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:612–27.