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Can oral cancer screening reduce late-stage diagnosis, treatment delay and mortality? A population-based study in Taiwan

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ABSTRACT

Objective This study evaluates the effectiveness of Taiwan's nationwide oral cancer screening programme in reducing late-stage diagnosis, treatment delays and mortality.

Design A retrospective cohort study was conducted.

Setting The study utilized Nationally representative datasets, including the Cancer Registry, Oral Mucosal Screening and National Health Insurance databases in Taiwan.

Participants The study included patients with oral cancer diagnosed between 1 January 2010 and 31 December 2013, with follow-up through 31 December 2018. The final analysis included 16 430 patients.

Intervention The intervention was Taiwan's nationwide oral cancer screening programme which provides visual inspection and palpation of the oral mucosa.

Primary outcome measures The primary outcomes measured were late-stage diagnosis (stages III and IV), treatment delay (time from diagnosis to treatment >30 days) and all-cause mortality.

Results Oral cancer screening was statistically significantly associated with a reduced likelihood of late-stage diagnosis (adjusted OR (AOR)=0.85, 95% CI 0.80 to 0.91, p<0.01). However, screening was also associated with a higher likelihood of treatment delay (AOR=1.09, 95% CI 1.00 to 1.19, p=0.049). Taken together, the screening programme is associated with a slightly lower hazard of death (adjusted HR=0.94, 95% CI 0.89 to 0.99, p=0.01).

Conclusion While Taiwan's nationwide oral cancer screening programme effectively reduced late-stage diagnoses and mortality, barriers to timely treatment access remain. Ensuring prompt diagnosis and treatment following screening may further enhance the survival benefits of the programme.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses a large, nationally representative dataset, enabling robust analysis and generalisation of findings to the broader Taiwanese population.
⇒ This study follows patients from initial diagnosis through treatment and death, where applicable, within the study period, providing a comprehensive view into the continuum of care.
⇒ Potential selection bias due to the eligibility criteria for the oral cancer screening programme, which targets high-risk populations, may influence the observed outcomes. We have attempted to mitigate some of this bias by controlling for variables related to programme eligibility criteria.
⇒ The study's reliance on secondary data limits the availability of detailed information on screening results and follow-up referral processes before the confirmation of oral cancer, which restricts further investigation into the reasons for diagnostic and treatment delays.

INTRODUCTION

Oral cavity cancer (OCC) poses a significant global health challenge, with Taiwan reporting the highest incidence and mortality rates for this disease.[1–3] Late-stage diagnosis, defined as stage III and IV disease at the time of diagnosis, has consistently correlated with diminished survival outcomes and a lower quality of life.[4–6] Notably, 40%–50% of patients with OCC have late-stage diagnoses.[7–10]

In response to this pressing issue, the Taiwanese government initiated a nationwide oral cancer screening (OCS) programme in 2004, aiming to enhance the early detection of OCC. This programme provides visual inspection or palpation of the oral mucosa, specifically targeting individuals aged over 30 years who chew betel—a nut harvested from the Areca palm that is a stimulant but also increases risk of OCC—or who smoke cigarettes, along with indigenous individuals aged above 18 years. Betel (including betel nut and betel quid), tobacco and alcohol are all classified as class 1 carcinogens by the International Agency for Research on Cancer and represent independent risk factors for OCC.[11] Those with positive screening results receive follow-up care and are referred to

Table 1 Characteristics of patient with oral cancer by oral cancer screening

	All		Screen		Non-screen	
Total	16430	100%	8445	100%	7985	100%
Oral cancer screening						
Yes	8445	51.4%	–	–	–	–
No	7985	48.6%	–	–	–	–
Late-stage diagnosis						
Yes	6601	40.2%	3301	39.1%	3300	41.3%
No	9829	59.8%	5144	60.9%	4685	58.7%
Delay treatment						
Yes	3044	18.5%	1621	19.2%	1423	17.8%
No	13386	81.5%	6824	80.8%	6562	82.2%
Death						
Yes	5457	33.2%	2731	32.3%	2726	34.1%
No	10973	66.8%	5714	67.7%	5259	65.9%
Age						
≤45	3498	21.3%	1770	21.0%	1728	21.6%
46–64	9984	60.8%	5253	62.2%	4731	59.2%
≥65	2948	17.9%	1422	16.8%	1526	19.1%
Sex						
Male	14923	90.8%	8103	96.0%	6820	85.4%
Female	1507	9.2%	342	4.0%	1165	14.6%
Income						
Low	4183	25.5%	2082	24.7%	2101	26.3%
Medium	9206	56.0%	4875	57.7%	4331	54.2%
High	2535	15.4%	1241	14.7%	1294	16.2%
Unknown	506	3.1%	247	2.9%	259	3.2%
Residence						
Urban	15815	96.3%	8112	96.1%	7703	96.5%
Rural	615	3.7%	333	3.9%	282	3.5%
Chewed betel						
No	4771	29.0%	2097	24.8%	2674	33.5%
Yes	9515	57.9%	5244	62.1%	4271	53.5%
Unknown	2144	13.1%	1104	13.1%	1040	13.0%
Smoked cigarettes						
No	3079	18.7%	1109	13.1%	1970	24.7%
Yes	11339	69.0%	6298	74.6%	5041	63.1%
Unknown	2012	12.3%	1038	12.3%	974	12.2%
Drank alcohol						
No	5215	31.7%	2458	29.1%	2757	34.5%
Yes	9065	55.2%	4884	57.8%	4181	52.4%
Unknown	2150	13.1%	1103	13.1%	1047	13.1%
Comorbidity						
CCI=0	8571	52.2%	4575	54.2%	3996	50.0%
CCI=1	2001	12.2%	1267	15.0%	734	9.2%
CCI=2	3272	19.9%	1459	17.3%	1813	22.7%
CCI=3	1280	7.8%	578	6.8%	702	8.8%
CCI≥4	1306	8.0%	566	6.7%	740	9.3%
Primary subsite						

Continued

Table 1 Continued

	All		Screen		Non-screen	
Lips	1079	6.6%	543	6.4%	536	6.7%
Tongue	5583	34.0%	2729	32.3%	2854	35.7%
Gum	2107	12.8%	1005	11.9%	1102	13.8%
Floor of mouth	537	3.3%	297	3.5%	240	3.0%
Palate and others	7124	43.4%	3871	45.8%	3253	40.7%

CCI, Charlson Comorbidity Index.

government-accredited cancer hospitals for the confirmation of OCC and subsequent treatment.

In addition to a delay in diagnosis, patients with OCC might also face treatment delays following their initial diagnosis. A longer time interval from diagnosis to treatment leads to worse survival.[11–15] Understanding how the healthcare delivery system operates for patients with OCC after OCS is essential to ensure the survival benefits of early diagnosis and timely treatment. Therefore, our objective is to evaluate the effectiveness of OCS in reducing late-stage diagnosis and treatment delay and in improving survival by leveraging data from the national Taiwanese cancer registry and screening databases.

MATERIALS AND METHODS

Study population

This retrospective cohort study of incident patients with OCC uses the Taiwanese National Cancer Registry database for patient care between 1 January 2010 and 31 December 2013. This nationwide cancer registry database covers over 97% of patients with OCC in Taiwan and contains cancer diagnosis and treatment information.[3] Patients with unknown pathological stages during the study period and missing zip codes were excluded (in total, about 2.8% of the sample was excluded).

Data

The study subjects were selected from the cancer registry database and linked to the Oral Mucosal Screening database to extract the patient's screening record that occurred prior to the initial diagnosis date. To analyse patients' survival, we then linked the data to the death registry database with follow-up conducted until 31 December 2018. Patient demographic and disease characteristics were sourced from the census database and the National Health Insurance database. After excluding 467 patients with missing zip codes, unknown pathological stages, or cancer recurrence, a total of 16430 incident patients with OCC were included in the analysis.

Dependent variables

The last-stage diagnosis was defined by the initial pathological confirmed cancer stage of OCC according to the American Joint Committee on Cancer Cancer Staging Manual (seventh edition). This study categorised stages III and IV as late stage and stages I and II as early stage. The treatment delay was based on the time interval between the initial diagnosis date and the initial treatment date. Treatment delay was defined as a diagnosis-to-treatment time interval above 30 days. This threshold was chosen based on previous studies in Taiwan, which demonstrated that a diagnosis-to-treatment interval longer than 30 days is associated with increased mortality.[13 14] Survival was defined as the 5-year survival from the initial diagnosis to the date of all-cause death or the end of the 5-year follow-up period.

Independent variables

The nationwide cancer screening programme in Taiwan is a biennial oral mucosal examination for cigarette smokers and betel chewers. OCS was defined as a screening record within 2 years before the initial diagnosis date of OCC.

Control variables

We controlled for demographic characteristics, high-risk behaviours and disease characteristics. Demographic characteristics included age (below 45, 46–64 and above 65), residence (rural or urban) and sex (male or female). Income status was classified into low (below 17280 New Taiwan Dollars (NTD) which was about US$582 based on an average exchange rate in 2013 of 1 NTD = US$0.0337[16]), medium (US$582–1947), and high (above US$1947).

High-risk behaviour included indicator variables for chewing betel, smoking cigarettes and drinking alcohol. Chewing betel, smoking cigarettes and drinking alcohol were based on baseline behaviours measured before the OCC initial pathological confirmation date and categorised into three groups (no, yes and unknown). Disease characteristics included comorbidity and primary subsite (lip (International Classification of Diseases, 10th Revision (ICD-10) code C00), tongue (ICD-10 codes C01-02), gum (ICD-10 code C03), floor of mouth (ICD-10 code C04), and palate and others (ICD-10 code C05-06)). Comorbidity was defined as whether patients have a disease record according to the Charlson Comorbidity Index using Deyo's method that aggregates the comorbidity diagnosis 1 year before the OCC initial diagnosis date. Additionally, the cancer stage at diagnosis was controlled in the time-to-treatment model since advanced cancer stages generally have longer wait times.[14 15] It was

Table 2 Unadjusted estimates on late stage, treatment delay and mortality among patients with oral cancer

	Late stage			Treatment delay			Mortality		
	COR	95% CI	P value	COR	95% CI	P value	CHR	95% CI	P value
Oral cancer screening									
No (reference)									
Yes	0.91**	0.86 to 0.97	<0.01	1.10*	(1.01 to 1.19)	0.02	0.93**	(0.88 to 0.98)	<0.01
Age									
≤45 (ref)									
46–64	1	(0.92 to 1.08)	0.99	1	(0.91 to 1.10)	0.99	1.07	(0.99 to 1.14)	0.07
≥65	0.83**	(0.75 to 0.92)	<0.01	0.93	(0.82 to 1.06)	0.28	1.57**	(1.45 to 1.71)	<0.01
Sex									
Male (ref)									
Female	0.79**	(0.71 to 0.88)	<0.01	0.99	(0.86 to 1.13)	0.82	0.82**	(0.74 to 0.91)	<0.01
Income									
High (ref)									
Medium	1.24**	(1.13 to 1.36)	<0.01	1.19**	(1.04 to 1.35)	<0.01	1.26**	(1.16 to 1.37)	<0.01
Low	1.62**	(1.46 to 1.80)	<0.01	1.06	(0.94 to 1.19)	0.36	1.45**	(1.32 to 1.58)	<0.01
Unknown	3.68**	(3.01 to 4.50)	<0.01	1.43**	(1.13 to 1.80)	<0.01	9.29**	(8.20 to 10.53)	<0.01
Residence									
Urban (ref)									
Rural	1.18	(1.00 to 1.39)	0.05	0.89	(0.71 to 1.11)	0.3	1.30**	(1.15 to 1.48)	<0.01
Chewed betel nut									
No (ref)									
Yes	1.31**	(1.22to 1.41)	<0.01	0.94	(0.85 to 1.04)	0.21	1.01	(0.95 to 1.07)	0.84
Unknown	1.43**	(1.29–1.59)	<0.01	4.51**	(4.01 to 5.07)	<0.01	0.99	(0.90 to 1.08)	0.79
Smoked cigarette									
No (ref)									
Yes	1.35**	(1.24 to 1.47)	<0.01	1.06	(0.94 to 1.18)	0.35	1	(0.94 to 1.08)	0.92
Unknown	1.57**	(1.40 to 1.76)	<0.01	5.39**	(4.71 to 6.17)	<0.01	0.99	(0.90 to 1.09)	0.84
Drank alcohol									
No (ref)									
Yes	1.31**	(1.22 to 1.41)	<0.01	0.95	(0.86 to 1.04)	0.27	1.17**	(1.11 to 1.25)	<0.01
Unknown	1.45**	(1.30 to 1.60)	<0.01	4.78**	(4.26 to 5.36)	<0.01	1.07	(0.97 to 1.16)	0.17
Comorbidity									
CCI=0 (ref)									
CCI=1	0.78**	(0.71 to 0.87)	<0.01	1.03	(0.92 to 1.17)	0.58	1.10*	(1.00 to 1.20)	0.04
CCI=2	0.61**	(0.56 to 0.66)	<0.01	0.65**	(0.58 to 0.72)	<0.01	1.38**	(1.28 to 1.47)	<0.01
CCI=3	0.58**	(0.51to 0.66)	<0.01	0.71**	(0.60 to 0.83)	<0.01	1.50**	(1.37 to 1.65)	<0.01
CCI≥4	0.77**	(0.68 to 0.87)	<0.01	0.72**	(0.61 to 0.84)	<0.01	2.21**	(2.03 to 2.40)	<0.01
Primary subsite									
Tongue (C01-02) (ref)									
Lips (C00)	0.43**	(0.37 to 0.50)	<0.01	1.03	(0.87 to 1.22)	0.76	0.84**	(0.74 to 0.94)	<0.01
Gum (C03)	2.79**	(2.5 to 3.09)	<0.01	1.17*	(1.03 to 1.33)	0.02	1.23**	(1.13 to 1.33)	<0.01
Floor of mouth (C04)	1.02	(0.85 to 1.23)	0.83	1.65**	(1.34 to 2.03)	<0.01	1.11	(0.96 to 1.29)	0.15
Palate and others (C05–C06)	1.09*	(1.01 to 1.17)	0.02	1.07	(0.98 to 1.18)	0.13	0.94*	(0.88 to 0.99)	0.03
Stage at diagnosis									
Early (ref)	–	–	–						
Late	–	–	–	1.60**	(1.48 to 1.74)	<0.01	2.79**	(2.65 to 2.95)	<0.01

Continued

Table 2 Continued

	Late stage			Treatment delay			Mortality		
	COR	95% CI	P value	COR	95% CI	P value	CHR	95% CI	P value
Treatment delay									
No (reference)									
Yes	–	–	–	–	–	–	1.22**	(1.15 to 1.31)	<0.01

N=16 430. * P<0.05, ** p<0.01.
CCI, Charlson Comorbidity Index; CHR, crude HR; COR, crude OR.

not controlled in the mortality model since doing so would control potential improvements in mortality stemming from earlier detection.

Statistical analyses

Univariable and multivariable analyses were conducted in a two-level hierarchical generalised linear mixed model. Each model included a Variance Inflation Factor test. The Cox proportional hazards model was used to assess differences in survival. This study regarded a p value <0.05 as statistically significant. SAS V.9.4 was used for data management and statistical analyses.

Patient and public involvement statement

Patient and public involvement were not applicable in this study. All data were deidentified and encrypted by the Taiwanese government. Consequently, we were unable to involve patients or the public in the design, conduct, reporting or dissemination of our research.

RESULTS

A total of 16 430 incident patients with OCC were included, of which 51.4% had undergone screening before diagnosis, 40.2% had a late-stage diagnosis, 18.5% experienced treatment delays and the mortality rate was 33.2%. The majority of patients were men (90.8%), were aged between 46 and 64 years (60.8%), had a medium income (56.0%), resided in urban areas (96.3%) and engaged in high-risk behaviours such as smoking (69.0%), alcohol consumption (55.2%) and betel chewing (57.9%). About 52.2% had no comorbidity prior to diagnosis (table 1).

Compared with non-screened patients, those who had undergone OCS were more likely to be male (96.0% vs 85.4%), to chew betel nut (62.1% vs 53.5%), to smoke cigarettes (74.6% vs 63.1%) and to consume alcohol (57.8% vs 52.4%) (table 1). These differences reflect the eligibility criteria for OCS and were controlled for in the multivariate analysis.

Patients who had undergone screening had a lower rate of late-stage diagnosis (39.1%) compared with those without screening (41.3%) (table 1). The univariate estimates revealed that screening was associated with a reduced likelihood of a late-stage diagnosis (95% CI: crude OR (COR)=0.91, 0.86 to 0.97, p<0.01) (table 2). After including covariates, patients with screening were 0.85 times less likely to be diagnosed at a late stage (95% CI 0.80 to 0.91, p<0.01) (table 3). However, patients undergoing screening had a higher rate of treatment delay (19.2%) compared with those without screening (17.8%) (table 1). Prior to adjusting for control variables, patients with screening were more likely to experience treatment delays (COR=1.10, 95% CI 1.01 to 1.19, p=0.02) (table 2). This finding aligns with the multivariate analysis, indicating that patients with screening were 1.09 times more likely to experience treatment delays (95% CI 1.00 to 1.19, p=0.0496) (table 3).

Screening populations have slightly lower mortality rates than the unscreened population: 32.3% versus 34.1% (table 1). Before controlling for covariates, patients with OCC undergoing screening exhibited a lower risk of death (crude HR (CHR)=0.93, 95% CI 0.88 to 0.98, p<0.01) (table 2). This trend persisted in the controlled regression model, with patients with OCC undergoing screening having a 0.94 times hazard of death (95% CI 0.89 to 0.99, p=0.01) (table 3). The adjusted model further indicated that treatment delay in general was associated

Table 3 Adjusted estimates on late stage, treatment delay and mortality among patients with oral cancer

	Late-stage			Treatment delay			Mortality		
	AOR	95% CI	P value	AOR	95% CI	P value	AHR	95% CI	P value
Oral cancer screening	**0.85****	0.80 to 0.91	<0.01	**1.09***	1.00 to 1.19	0.049	**0.94***	0.89 to 0.99	0.01
Treatment delay	–	–	–	–	–	–	**1.13****	1.06 to 1.21	<0.01

Notes: n=16 430. *P<0.05, **p<0.01. Each model was adjusted by age, sex, income, whether chewed betel nuts, whether smoked cigarettes, whether drank alcohol, comorbidity and primary subsite. The treatment delay outcome additionally controlled the cancer stage at diagnosis.
AHR, adjusted HR; AOR, adjusted OR; CCI, Charlson Comorbidity Index.

with a 1.13 times higher hazard of death (95% CI 1.06 to 1.21, p<0.01) (table 3).

DISCUSSION

Our study provides evidence on the association between OCS and reduced late-stage diagnoses[17 18] and its expected role in improving mortality.[13] Surprisingly, patients who underwent screening were also more likely to experience treatment delays, which can worsen mortality. One potential explanation for screening-associated treatment delays is that only 45.98% of the facilities where OCC is diagnosed are also certified to treat OCC. Additionally, 80% of OCC care facilities in Taiwan's largest county with the highest OCC incidence only provide diagnostic services.[19] Consequently, the additional time required to refer patients with OCC to treatment-certified facilities might contribute to treatment delays.[11 20] While the net effect of these countervailing results was increasing mortality, improving timely treatment access among the screening population may help to realise the full benefit of OCS.

One study based on 13 years of follow-up real-world data reveals that the cost of Taiwan's OCS programme is US$4.34 per person, with an incremental cost-effectiveness ratio of US$28 516 per life year, which exceeds 1 Gross Domestic Product (GDP) per capita per life-year saved. This study also emphasises that a higher early detection rate can enhance cost-effectiveness.[21] Our findings further underscore the importance of timely treatment for patients with OCC following screening. Reducing treatment delays after screening may also improve the cost-effectiveness of the OCS programme. To maximise the benefits of OCS, the Taiwanese government may consider monitoring the supply and demand of diagnostic and treatment-certified facilities and ensure adequate capacity and care delivery to prevent treatment delays.

To our knowledge, this is the first study to identify the issue of treatment delay among patients with OCC undergoing screening. Our study provides evidence that supports strategies to improve the effectiveness of OCS by ensuring timely treatment. Additionally, the study uses a large, nationally representative dataset, enabling robust analysis and generalisation of findings to the broader Taiwanese population. Finally, by following patients from initial diagnosis through treatment and up to death within the study period, this research provides a comprehensive understanding of the entire care delivery process.

Several limitations should be acknowledged in this study. Foremost among them is the potential selection bias of the eligibility criteria for OCS, which targets high-risk populations including betel chewers and alcohol consumers, combined with the self-selection of eligible patients to receive OCS. We have attempted to address this issue by controlling for high-risk behaviours including betel chewing, smoking and alcohol consumption, as well as other demographic and disease characteristics. However, this potential selection bias issue would likely serve to attenuate the results towards zero given that the screening population would potentially be in poorer health. Despite this, we still measure statistically significant effects. Additionally, the causes of OCC diagnostic and treatment delay may involve factors related to patients, healthcare professionals or healthcare services.[22] Our data lack detailed information on screening results, diagnosis confirmation and follow-up referral details.

Overall, this nationwide study suggests that the OCS programme was associated with reductions in OCC later-stage diagnoses and mortality. However, given longer delays in treatment among patients who were screened, even more mortality gains may be relatively readily achievable. Ensuring timely access to care in all phases of the patient's journey from screening through treatment is essential for the benefits of this programme to be fully realised.

Contributors ET: writing-original draft, investigation, conceptualisation, methodology, formal analysis, software. BW: conceptualisation, methodology, validation, writing - review and editing. S-CW: conceptualisation, validation, supervision, funding acquisition. S-CW is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Institutional Review Board of National Yang-Ming University (IRB approval number: 1070601-2). The data used in this study were de-identified and encrypted by the Health and Welfare Data Science Center at the Ministry of Health and Welfare to ensure personal data protection.

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Data availability statement No data are available.

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