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Finding an oral potentially malignant disorder in screening program is related to early diagnosis of oral cavity cancer – Experience from real world evidence

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ABSTRACT

Objectives: Our study evaluates the effectiveness of the Taiwan Oral Mucosal Screening (TOMS) program in stage-shift among oral cavity cancer patients, and identifies the related factors with early cancer diagnosis.
Materials and methods: This retrospective cohort study used the Taiwan Cancer Registry (TCR), TOMS and Taiwan Death Registry (TDR) databases. We identified oral cavity cancer patients (ICD-C-O: C00-C06) from the TCR during 2012–2015. Patients' screening history, first screening status and subsequent screenings were analyzed with cancer stages and survival outcomes.
Results: The 5-year survival rates for stages 0–4 were 83.9%, 82.1%, 72.7%, 60.1% and 38.0%. Among 18,625 patients identified from the TCR, 37% did not have any prior screenings. Patients with prior positive or negative screenings all had better survival rates (3-year: 71.4% and 68.7% vs. 63.5%, Log-rank p-value < 0.0001). The best chance for early-stage diagnosis occurs in oral potentially malignant disorder (OPMD, OR = 1.99, 95% CI = 1.78–2.22, $p < 0.0001$) patients at their first screenings. The hazard ratios (HR) for patients with prior screenings indicated a significant survival benefit. The group of incomplete diagnosis confirmation also has better survival (HR = 0.78, 95% CI = 0.81–0.93, $p < 0.0001$), and a greater chance of early diagnosis at subsequent screenings.
Conclusion: While TOMS improved stage-shift for early cancer diagnosis, we found no obvious differences in participants with cancers at screening (stages 0–1: 26.3% vs. 27.8% in non-screening group). Survival benefit and early diagnosis are found in most of screening groups, and identifying an OPMD is particularly essential to early diagnosis of oral cavity cancer patients.

Introduction

Oral cancer has been a major health burden for populations with high prevalence of areca/betel quid chewing. In 2018, it was estimated 354,864 lip and oral cavity (ICD-O-3: C00-C08) patients and 177,384 deaths worldwide [1]. While chewing areca/betel quid is common in the South-Central and South-East Asia, the two regions alone have 176,568 (50%) lip and oral cavity cancer cases and 107,393 (61%) deaths given that their population is only roughly 34% of the world population [1]. Despite the fact that lip and oral cavity sites are relatively easy to examine, it was reported that only about one-third or less of oral cancer patients were detected in the early stages [2,3], and around 50% of patients were still presented in advanced stages [4]. Patients whose cancer diagnosis occurrs in later stages often have high mortality [5], and the 5-year survival rates generally vary from greater than 80% for patients diagnosed in early stages to approximately 60% or less for late stages [2–4].

Evidence has shown that screening reduces mortality in the high-risk group with a stage-shift at the time of diagnosis [5]. A cluster-randomized controlled trial from India showed that routine oral visual screening could reduce more than 30% mortality rate in the high-risk population [6]. A follow-up study in Taiwan for population-based cancer screening program [7] also indicated a 13% higher survival rate for cancers detected during screenings than for clinically detected cancers.

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Oral cancer is a serious problem in Taiwan due to high prevalence of areca/betel quid chewing habits in certain populations [8]. The age-standardized oral cancer incidences (ICD-O-3: C00-C06) in 2015 were 31.16 and 3.03 per 100,000 for males and females, and the corresponding mortalities were 9.85 and 0.92 per 100,000 [9]. The Taiwan Oral Mucosal Screening Program (TOMS) is an organized population-based screening program to reduce oral cancer mortality. The TOMS program includes opportunistic screening as well as outreach screening to at-risk populations. Biennial screenings are recommended for high-risk groups (such as people with betel quid chewing or smoking habits). Despite the fact that screening services are available in many medical institutes, the challenge is still remained. It has been highlighted by studies that these high-risk individuals usually do not seek out health services or do so less frequently [10]. Therefore, the effectiveness of identifying patients at early stages remains a challenge for opportunistic screening.

The TOMS database has been available to researchers since 2010. Together with the Taiwan Cancer Registry (TCR) and Death Registry (TDR), this has made feasible the comparison of screening and non-screening cases for oral cancer patients using real world evidence. In terms of monitoring the implementation of the TOMS program, it is important to continuously evaluate the effectiveness of the screening program as well as factors related to a higher chance of patients diagnosed at early stages. The first objective of our study was to evaluate the effectiveness of the TOMS program in stage-shift among oral cavity cancer patients between screening and non-screening cases. We also try to identify the related factors to early stage cancer diagnosis.

Materials and methods

Data source

This retrospective cohort study used the Taiwan Cancer Registry (TCR), Taiwan Oral Mucosal Screening (TOMS) and Taiwan Death Registry (TDR) databases. Data management and statistical analyses were performed in the Health and Welfare Data Science Center (HWDC), which is managed by the Department of Statistics, Taiwan Ministry of Health and Welfare. The HWDC provides government databases for research use. To protect privacy, all identifying personal information is encrypted, only authorized researchers are permitted to access the databases in a designated area, and only statistical results are allowed to be carried out for publications. This study was granted with ethics approval from the Institutional Review Board (IRB) of Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT(II)20170014), and the need for informed consent was waived by the IRB.

The TCR database was established for cancer surveillance and control in 1979 [11]. Since 2002, hospitals with 50 or more beds began to report 20 (short form) to 65 (long form) items for monitoring cancer care quality. The long form, which contains the core information of cancer diagnosis and first primary treatment, was further extended to 95 items in 2007 and 114 items in 2011 for some major cancers. Oral cavity and pharynx cancer have been in the long form registry since 2004.

Although population-based oral mucosal screening has been implemented since 2004, the current screening database in the Health and Welfare Data Science Center was established in 2010. The TOMS database consists of participants' basic information on betel quid chewing and smoking habits, the results of oral visual inspection by trained physicians and dentists, and specialists' confirmation and biopsy reports for referrals. The TOMS program recommends biennial screening for high-risk groups (people with betel quid chewing or smoking habits). If any target oral potentially malignant disorders (OPMDs) were identified, patients are subsequently followed for every 3–6 months. The TDR was also adapted to identify the cause of death.

We extracted two cohorts to meet our study objectives. The first cohort was used to compute the stage-specific survival rates. Within the TCR database, we first used the Cancer Registry Annual Report (HWDC filename: CRSSC) file to identify oral cavity cancer patients from 2008–2015. This file contains records for statistics documented in the TCR annual report. We used ICD-C-O (C00-C06) to identify oral cavity cancer patients and then included patients with cancer diagnosis dates during the period 2008–2015. We excluded patients whose histology indicated lymphoma, Hodgkin lymphoma and non-Hodgkin lymphoma. These oral cavity patients were further linked to TDR untill 2016.

The second cohort was used for the retrospective cohort study. The TOMS database was initiated in 2010, and the screening interval was every 2 years. To allow for a full 2-year observation period, we identified oral cavity cancer patients from the TCR annual report file for the period 2012–2015. Because the screening targeted betel quid chewers or cigarette smokers aged 30 years old or older. We also limited this cohort to patients with 30 years old or older. These patients were then linked to the TOMS database to extract their screening records prior to their cancer diagnosis, and they were linked to the TDR for dates and causes of death.

Analysis variables

The mortality outcomes include all-cause death and oral cavity cancer death. Any records identified from the TDR are considered all-cause death. We define any appearance of ICD-C-O (C00-C06) in the primary and secondary cause of death in the TDR as oral cavity cancer death.

In terms of screening status, two variables were defined to reflect patients' prior screening experience based on information retrieved from TOMS. The first variable is screening status: (1) patients with prior positive screening records, for patients who have one or more prior referral records; (2) patients without prior positive screening records, for patients who have screening records but all of the records were negatives; (3) patients who were not screened before cancer diagnosis, any patients who had no records of attending the TOMS program.

The second variable is the first screening records for oral cavity cancer patients. For patients with prior screening records, we retrieved their first screening records and classified these into 5 categories: (1) "confirmed cancer," for patients with confirmed specialist/pathological reports with records of carcinoma in situ, verrucous carcinoma, or squamucous carcinoma, (2) "confirmed OPMD," for patients with confirmed specialist/pathological reports with records of hyperplasia, hyperkeratosis, leukoplakia, erythroplakia, dysplasia, verrucous lesion, OSF, or lichen planus, (3) "confirmed non-OPMD," for patients with confirmed specialist/pathological reports without any of the above mentioned diseases indicated in the TOMS records, (4) "not confirmed," for patients who were screened positive, but did not complete diagnosis confirmation after referral, and (5) "not referred," for patients who were not referred after their first screening.

The follow-up duration was calculated from the date of cancer diagnosis (from the TCR) to the date of death (from the TDR) or to December 31, 2016 (end of follow-up time).

From the TCR, we were able to compute the age of cancer diagnosis and obtained the cancer stage and sites. For patients included in the TOMS, their betel quid chewing and cigarette smoking habits were also recorded. We identified the total number of subsequent screenings between first screening to the cancer diagnosis by linking the encrypted personal identification in the TOMS.

Statistical analysis

ANOVA and Chi-square test were conducted to compare numerical and categorical variables among comparison groups. The Kaplan-Meier estimates were presented for all-cause and oral cavity cancer specific survival rates. We defined stages 0–1 as early stage diagnosis outcome. Logistic regression was used to investigate the odds ratios of early stage diagnosis for different first screening results as well as the subsequent

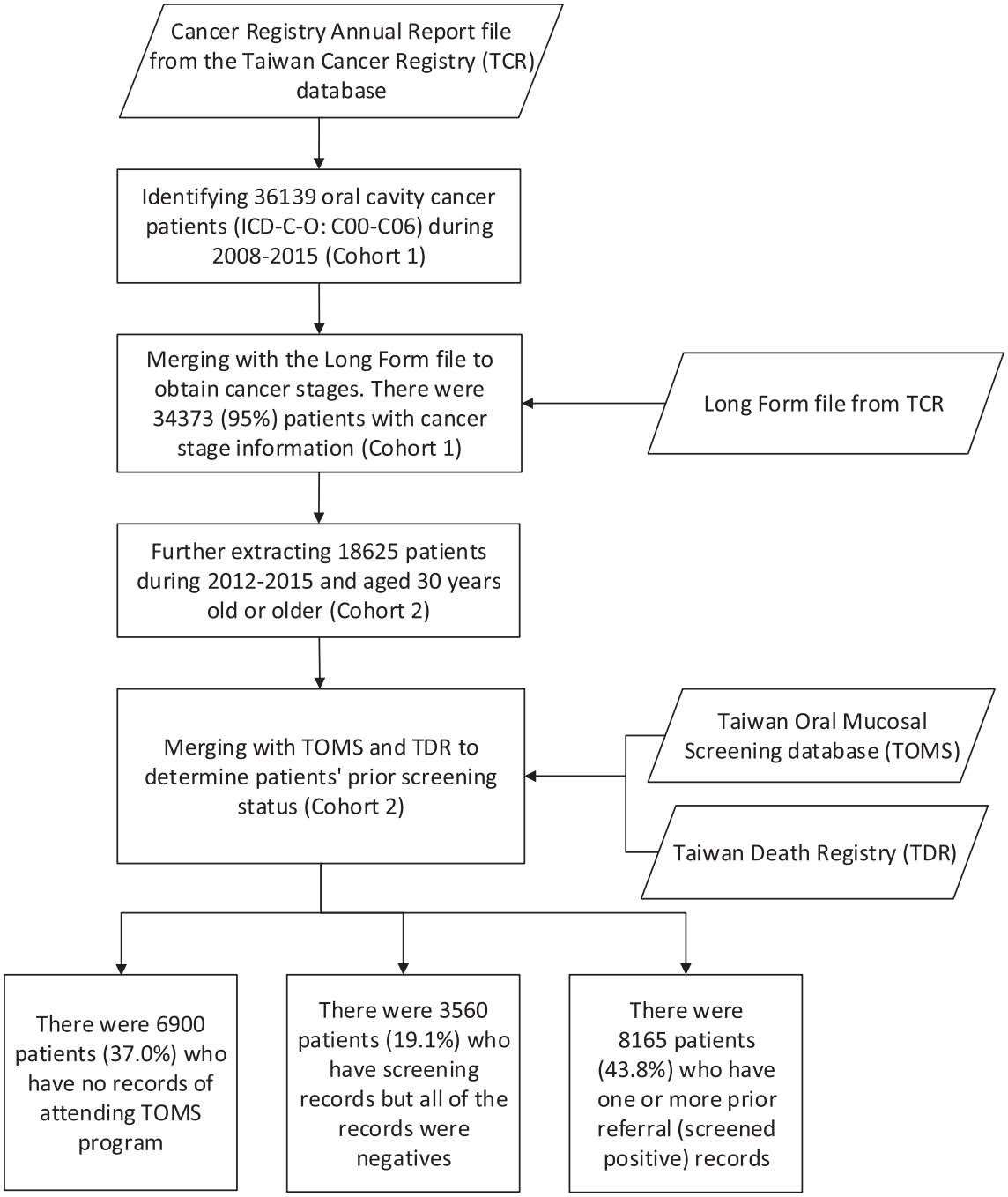

Fig. 1. Flowchart for extracting study cohorts from the databases. Parallelograms represent database inputs and rectangles represent process results.

number of screenings. The association between adjusted covariates and mortality was evaluated by both univariate and multivariable analyses using the Cox regression, and the results were presented in hazard ratios (HR) and 95% confidence intervals (CIs). All analyses and data management were conducted using SAS version 9.4 (SAS Institutes, Inc., Cary, NC, US).

Results

For the period 2008-2015, we identified 36,139 oral cavity cancer patients from the TCR database (Fig. 1), and cancer stages are found for 34,373 patients (95%) by linking to the Long Form of TCR. The stage-specific survival rates are shown in Table 1. The 5-year survival rates for stages 0–4 were 83.9%, 82.1%, 72.7%, 60.1% and 38.0%, respectively. The 3- and 5-year all cause survival rates for stage 0 and 1 were not very different (90.8% vs. 88.0% and 83.9% vs. 82.1%). From stage 1, the 5-year all-cause survival rates decreased 10% or more as the stages increased. Patients without stage information had a 5-year survival rate of 44.8%, which is between the rates for stages 3 and 4.

We further included patients aged 30 years old or older during the period 2012–2015, which represents a cohort parallel to the TOMS Program (Fig. 1). We identified 18,625 oral cavity cancer patients, of which 6900 patients (37.1%) did not have any screening records prior to their cancer diagnosis (Table 2). Patients with prior screening records, regardless of whether they were referred or not, tended to have better survival rates (3-year: 71.4% and 68.7% vs. 63.5%, Log-rank p-value < 0.0001). In terms of cancer sites, base of tongue (C01) had the highest percentage of no positive screening (33.7%) and followed by

Table 1
Stage-specific survival rates 2008-2015 computed from Taiwan Cancer Registry.

Stage	# of patients	% in stages	Median age of diagnosis	% of males	All cause death Survival rate		Oral cavity death Survival rate	
					3-year	5-year	3-year	5-year
0	275	0.8%	55	86.9%	90.8%	83.9%	97.1%	94.5%
1	10,383	30.2%	53	88.2%	88.0%	82.1%	92.3%	89.0%
2	6627	19.3%	54	91.1%	79.8%	72.7%	84.9%	80.4%
3	3954	11.5%	53	91.8%	68.8%	60.1%	74.6%	68.3%
4	13,134	38.2%	53	92.0%	45.4%	38.0%	52.1%	45.9%
Other*	1766		55	87.4%	51.7%	44.8%	63.3%	58.3%

Other*: no stage information.

floor of mouth (C04) (28.0%). Buccal (C06) (33.0%) had the highest percentage of being screened and referred. Comparisons of early stage diagnosis (stages 0–1), patients with prior screening recordsall had higher percentages (34.3% and 34.1%) than patients who were not screened (27.8%). These patients also had 44.5% in stage 4, which was about 10% more than the screening group.

For patients who had been screened, we investigated their clinical characteristics and habits based on their first screening status (Table 3). The highest 3-year all-cause survival rate was in the confirmed OPMD group (77.0%), while the confirmed cancer group had the lowest rate. For patients who were confirmed with cancer at their first screening, the proportions of early stages (26.3%) were similar to patients without any prior screening records (27.8%, Table 2). Only patients who were confirmed with OPMD or non-OPMD at their first screening records had greater percentages of early stages (42.0% and 40.9%). Patients who did not complete diagnosis confirmation ("not confirmed") had a 3-year survival rate of 71.3%, which is higher than non-screening patients (63.5%).

To investigate the association between subsequent screenings and early stage diagnosis, Table 4 shows that patients with 2 or more screenings tend to have a better chance of having an early-stage diagnosis. The differences were 10% or more in patients whose first screening status was non-OPMD, not confirmed and not referred. We also computed the same statistics in patients with at least 2-year follow-up between their first screening and cancer diagnosis, and the percentages of early stages were still higher in patients with 2 or more screenings. The median differences between 2 screenings were 642 to 702 days, which approximately followed the recommended 2-year interval. There were 27.7% to 32.9% of patients who did not attend subsequent routine screenings during the period between first screening and cancer diagnosis. For patients who did attend subsequent screenings, their proportions of early-stage diagnosis increased from 27.6% to

Table 2
Comparison of characteristics of 2012–2015 oral cavity cancer patients' screening history before cancer diagnosis.

		Total	No screened records[a]		Without prior positive[b]		With prior positive[c]		P-value
		N	N	%	N	%	N	%	
Total		18,625	6900	[37.1%]	3560	[19.1%]	8165	[43.8%]	
Sex	Female	1778	1235	(17.9%)	260	(7.3%)	283	(3.5%)	< 0.0001
	Male	16,847	5665	(82.1%)	3300	(92.7%)	7882	(96.5%)	
Age group	< 45	3319	1143	(16.6%)	542	(15.2%)	1634	(20.0%)	< 0.0001
	45 ~ 54	6029	2185	(31.7%)	1076	(30.2%)	2768	(33.9%)	
	55 ~ 64	5589	1971	(28.6%)	1108	(31.1%)	2510	(30.7%)	
	65+	3688	1601	(23.2%)	834	(23.4%)	1253	(15.3%)	
Survival rates for all-cause death	2-year			68.7%		73.3%		76.8%	< 0.0001
	3-year			63.5%		68.7%		71.4%	
Survival rates for oral cancer death	2-year			74.0%		79.0%		80.5%	< 0.0001
	3-year			70.2%		75.8%		76.6%	
Year of cancer diagnosis	2012	4561	1959	(28.4%)	725	(20.4%)	1877	(23.0%)	< 0.0001
	2013	4553	1773	(25.7%)	830	(23.3%)	1950	(23.9%)	
	2014	4797	1697	(24.6%)	986	(27.7%)	2114	(25.9%)	
	2015	4714	1471	(21.3%)	1019	(28.6%)	2224	(27.2%)	
Cancer diagnosis information	no	717	306	(4.4%)	134	(3.8%)	277	(3.4%)	0.004
	yes	17,908	6594	(95.6%)	3426	(96.2%)	7888	(96.6%)	
	stage								
	0 ~ 1	5705	1835	(27.8%)	1167	(34.1%)	2703	(34.3%)	< 0.0001
	2	3360	1151	(17.5%)	634	(18.5%)	1575	(20.0%)	
	3	1913	675	(10.2%)	373	(10.9%)	865	(11.0%)	
	4	6930	2933	(44.5%)	1252	(36.5%)	2745	(34.8%)	
	Site								
	Lip(C00)	945	327	[34.6%]	166	[17.6%]	452	[47.8%]	< 0.0001
	Base of tongue(C01)	905	381	[42.1%]	305	[33.7%]	219	[24.2%]	
	Other part of tongue(C02)	5676	2355	[41.5%]	1109	[19.5%]	2212	[39.0%]	
	Gum(C03)	2010	690	[34.3%]	402	[20.0%]	918	[45.7%]	
	Floor of mouth(C04)	572	187	[32.7%]	160	[28.0%]	225	[39.3%]	
	Palate(C05)	1289	505	[39.2%]	278	[21.6%]	506	[39.3%]	
	Buccal(C06)	6511	2149	[33.0%]	1006	[15.5%]	3356	[51.5%]	

Note: Percentages in parentheses are vertically sum up to 100%. Percentages in brackets are horizontally sum up to 100%.
[a] Patients with no records of attending TOMS program.
[b] Patients with screening records but all of the records were negatives.
[c] Patients with one or more prior referral (screened positive) records.

Table 3
Comparison of characteristics for patients' first screening status.

		Confirmed cancer		Confirmed OPMD		Confirmed non-OPMD		Not confirmed		Not referred		p-value
		n	%	n	%	n	%	n	%	n	%	
	Total	2631		1843		800		1335		5116		
Sex	Female	93	(3.5%)	53	(2.9%)	41	(5.1%)	42	(3.1%)	314	(6.1%)	< 0.0001
	Male	2538	(96.5%)	1790	(97.1%)	759	(94.9%)	1293	(96.9%)	4802	(93.9%)	
Age group	< 45	570	(21.7%)	366	(19.9%)	137	(17.1%)	283	(21.2%)	820	(16.0%)	< 0.0001
	45 ~ 54	966	(36.7%)	585	(31.7%)	252	(31.5%)	488	(36.6%)	1553	(30.4%)	
	55 ~ 64	772	(29.3%)	600	(32.6%)	277	(34.6%)	377	(28.2%)	1592	(31.1%)	
	65+	323	(12.3%)	292	(15.8%)	134	(16.8%)	187	(14.0%)	1151	(22.5%)	
Death	No	1805	(68.6%)	1438	(78.0%)	594	(74.3%)	969	(72.6%)	3650	(71.3%)	< 0.0001
	Yes	826	(31.4%)	405	(22.0%)	206	(25.8%)	366	(27.4%)	1466	(28.7%)	
Survival rates for all-cause death	2-year		74.0%		82.0%		78.3%		76.0%		73.9%	< 0.0001
	3-year		67.9%		77.0%		73.1%		71.3%		69.2%	
Cancer death	No	1948	(74.0%)	1527	(82.9%)	640	(80.0%)	1056	(79.1%)	4024	(78.7%)	< 0.0001
	Yes	683	(26.0%)	316	(17.1%)	160	(20.0%)	279	(20.9%)	1092	(21.3%)	
Survival rates for oral cavity cancer death	2-year		77.5%		84.8%		82.1%		80.4%		79.2%	< 0.0001
	3-year		72.8%		81.4%		77.9%		77.4%		76.0%	
Betel quid chewing habit#	None	319	(12.1%)	249	(13.5%)	123	(15.4%)	171	(12.8%)	1264	(24.7%)	< 0.0001
	Quit	1398	(53.1%)	951	(51.6%)	429	(53.6%)	597	(44.7%)	2233	(43.6%)	
	< 20 counts/day and < 10 years[a]	116	(4.4%)	87	(4.7%)	49	(6.1%)	82	(6.1%)	299	(5.8%)	
	≥20 counts/day and < 10 years[b]	37	(1.4%)	26	(1.4%)	8	(1.0%)	19	(1.4%)	61	(1.2%)	
	< 20 counts/day and ≥10 years[c]	256	(9.7%)	215	(11.7%)	76	(9.5%)	182	(13.6%)	608	(11.9%)	
	≥ 20 counts/day and ≥10 years[d]	505	(19.2%)	315	(17.1%)	115	(14.4%)	284	(21.3%)	651	(12.7%)	
Cigarette smoking habit#	None	160	(6.1%)	121	(6.6%)	66	(8.3%)	96	(7.2%)	420	(8.2%)	< 0.0001
	Quit	430	(16.3%)	368	(20.0%)	163	(20.4%)	183	(13.7%)	1014	(19.8%)	
	< 20 cigarettes/day and < 10 years[e]	149	(5.7%)	114	(6.2%)	46	(5.8%)	68	(5.1%)	439	(8.6%)	
	≥20 cigarettes/day and < 10 years[f]	41	(1.6%)	24	(1.3%)	4	(0.5%)	25	(1.9%)	103	(2.0%)	
	< 20 cigarettes/day and ≥10 years[g]	625	(23.8%)	460	(25.0%)	204	(25.5%)	370	(27.7%)	1437	(28.1%)	
	≥20 cigarettes/day and ≥10 years[h]	1226	(46.6%)	756	(41.0%)	317	(39.6%)	593	(44.4%)	1703	(33.3%)	
Cancer diagnosis information	No	68	(2.6%)	66	(3.6%)	39	(4.9%)	52	(3.9%)	186	(3.6%)	0.018
	Yes	2563	(97.4%)	1777	(96.4%)	761	(95.1%)	1283	(96.1%)	4930	(96.4%)	
	Stage											
	0 ~ 1	673	(26.3%)	746	(42.0%)	311	(40.9%)	402	(31.3%)	1738	(35.3%)	< 0.0001
	2	520	(20.3%)	343	(19.3%)	142	(18.7%)	301	(23.5%)	903	(18.3%)	
	3	305	(11.9%)	180	(10.1%)	83	(10.9%)	134	(10.4%)	536	(10.9%)	
	4	1065	(41.6%)	508	(28.6%)	225	(29.6%)	446	(34.8%)	1753	(35.6%)	
	Site											
	Lip(C00)	127	(5.0%)	117	(6.6%)	53	(7.0%)	77	(6.0%)	244	(4.9%)	< 0.0001
	Base of tongue(C01)	64	(2.5%)	52	(2.9%)	21	(2.8%)	24	(1.9%)	363	(7.4%)	
	Other part of tongue(C02)	752	(29.3%)	439	(24.7%)	218	(28.6%)	338	(26.3%)	1574	(31.9%)	
	Gum(C03)	281	(11.0%)	231	(13.0%)	77	(10.1%)	144	(11.2%)	587	(11.9%)	
	Floor of mouth(C04)	82	(3.2%)	36	(2.0%)	21	(2.8%)	26	(2.0%)	220	(4.5%)	
	Palate(C05)	172	(6.7%)	105	(5.9%)	53	(7.0%)	70	(5.5%)	384	(7.8%)	
	Buccal(C06)	1085	(42.3%)	797	(44.9%)	318	(41.8%)	604	(47.1%)	1558	(31.6%)	

Note: Percentages in parentheses are vertically sum up to 100%.
[a] Chewing less than 20 counts per day for less than 10 years.
[b] Chewing more than 20 counts per day for less than 10 years.
[c] Chewing less than 20 counts per day for more than 10 years.
[d] Chewing more than 20 counts per day for more than 10 years.
[e] Smoking less than 20 cigarettes per day for less than 10 years.
[f] Smoking more than 20 cigarettes per day for less than 10 years.
[g] Smoking less than 20 cigarettes per day for more than 10 years.
[h] Smoking more than 20 cigarettes per day for more than 10 years.

32.7% (one additional screening, difference = 5.1%) and 48.3% (two or more additional screenings, difference = 20.6%).

The effects of subsequent follow-up screenings were further investigated by logistic regressions (Table 5). In model 1, the logistic regression revealed odds ratios (OR) for being diagnosed at early stages at different first screening status. Patients who were confirmed as OPMD had the highest chance of being diagnosed at early stages (OR = 1.99, 95% CI = 1.78–2.22, p < 0.0001), followed by patients with confirmation of non-OPMD (OR = 1.85, 95% CI = 1.59–2.15, p < 0.0001). The OR of patients being confirmed as cancer at screenings was 1.00 (95% CI = 0.90–1.11, p = 0.9632). When considering frequency of screenings (model 2), the confirmed OPMD group

Table 4
Association of follow-up visits with early stage diagnosis at patients' first screening status.

Variable		N	Confirmed OPMD				Confirmed non-OPMD				Not confirmed				Not referred			
			Mean (SD)	Median			Mean (SD)	Median			Mean	Median			Mean (SD)	Median		
			N (%)	Stages 0–1[a] N (%)	Increased[b]		N (%)	Stages 0–1[a] N (%)	Increased[b]		N (%)	Stages 0–1[a] N (%)	Increased[b]		N (%)	Stages 0–1[a] N (%)	Increased[b]	
Interval between 2 screenings (days)		780	672 (378)	642			678 (413)	663			731 (392)	702			694 (379)	665		
Days of first screening to cancer diagnosis		1843	701 (546)	632			697 (595)	613			761 (562)	723			840 (531)	804		
Days of last screening to cancer diagnosis		1843	343 (407)	198			345 (425)	154			384 (449)	216			415 (441)	294		
Frequency of screening before cancer diagnosis	1		1036	407 (39.3)			462	178 (38.5)			753	194 (25.8)			2604	815 (31.3)		
	2		571	240 (42.0)	2.7%		247	89 (36.0)	−2.5%		458	148 (32.3)	6.6%		1828	630 (34.5)	3.2%	
	≥3		216	91 (42.1)	2.8%		91	44 (48.4)	9.8%		124	60 (48.4)	22.6%		684	293 (42.8)	11.5%	
Frequency of screening before cancer diagnosis (Limited to patients whose first screening to diagnosis were more than 2 years)	1		229 (27.7)	82 (35.8)			107 (29.1)	45 (42.1)			217 (32.9)	60 (27.6)			849 (30.4)	278 (32.7)		
	2		394 (47.6)	169 (42.9)	7.1%		181 (49.2)	70 (38.7)	−3.4%		327 (49.5)	107 (32.7)	5.1%		1324 (47.4)	460 (34.7)	2.0%	
	≥3		204 (24.7)	87 (42.6)	6.8%		80 (21.7)	38 (47.5)	5.4%		116 (17.6)	56 (48.3)	20.6%		622 (22.3)	272 (43.7)	11.0%	

[a] # diagnosed at stages 0–1.
[b] % increased of stages 0–1 for more than 1 follow-up screening.

had a significantly better chance of diagnosis at early stages. Patients with first screening status of not confirmed and not referred had a significantly better chance of diagnosis at early stages with 2 or more follow-up screenings (ORs = 1.38, 2.76, 1.18 & 1.67, $p < 0.05$).

Table 6 shows the hazard ratios (HR) for all-cause death and oral cavity specific death. All of the groups of first screening status showed significant survival benefit. The confirmed OPMD group had the lowest risk (all-cause HR = 0.71, 95% CI = 0.63–0.78, $p < 0.0001$; oral cavity HR = 0.72, 95% CI = 0.64–0.81, $p < 0.0001$). The group of not confirmed also showed significant survival benefit (HR = 0.78, 95% CI = 0.81–0.93, $p < 0.0001$).

Discussion

Our study combines three government databases (screening, cancer and death registries) to obtain real world evidence for the effectiveness of the TOMS program for mortality reduction as well as early-stage diagnosis. Our results show that 62.9% of oral cavity cancer patients were previously screened by the TOMS, and these patients did have more early stage (stages 0–1) and less late stage (stages 3–4) cases. However, when considering the individual screening diagnosis, the proportion of early stages in patients who were confirmed with cancer at their first screening is similar to cancer patients without any prior screenings (26.3% vs. 27.8%). There does not appear to be any obvious stage-shift when participants present to screening with cancers. The better chance of early stage diagnosis occurs in patients who were confirmed with OPMD (OR = 1.99, 95% CI = 1.78–2.22, $p < 0.0001$) or non-OPMD (OR = 1.85, 95% CI = 1.59–2.15, $p < 0.0001$) at their first screenings.

Mortality reduction in cancer-screening program is primarily due to cancer being discovered at early stages. Our results from Cancer Registry show a 44% and 22% difference in 5-year survival rates between stages 4 (38.0%) and 3 (60.1%) vs. stage 1 (82.1%). A study in India showed a 22% reduction in oral cancer mortality. Although survival benefit was not directly proven, a significant mortality 34% reduction was reported in high-risk groups after 9 years of follow-up, and a persistent 24% reduction in oral cancer mortality was found after 15 years of follow-up [12]. In a study of Cuba's oral cancer screening [13], the stage 1 oral cancer detection rate rose from 22.8 to 48.2% after the intervention of a screening program. The detection rate for stage 1 oral cancer rose from 22.8% to 42.2% in the screening program [14]. In Taiwan [7], there was a 5% increase of early diagnosis in stages 0-1 for the screening group compared to the non-screening group and a significant mortality reduction in high-risk groups. Our results confirm the effectiveness of screening programs in improving survival rates for oral cavity cancer patients. The cancer cases with prior positive screening results showed an 8% benefit in 2- and 3-year survival rates. We found that the major contribution for stage-shift and mortality reduction is from the screening diagnosis of OPMDs, so, although any cancer diagnosis would require immediate medical attention, it is also important to ensure follow-ups on any detected OPMDs. In TOMS program, patients with OPMDs would be treated through regular medical care, and it is recommended that patients need to be followed for at least every 3–6 months. From our results, the median days of last screening to cancer is 198 days, which is consistent with this recommendation.

The oral cavity has the advantage of easy access for visual and palpation examination, which are considered noninvasive and less expensive [15–19]. The potential for screening of oral cancer exist as there are recognized at premalignant phases of the disease [20]. Screening is generally defined as identifying an unrecognized disorder in individuals without signs or symptoms [4], which is not intended to be diagnostic. The effectiveness of screening focuses not only on the test itself and is primarily affected by the whole implementation program [21]. Earlier studies [10,22,23] reported that the compliance with further confirmation examination was between 54% and 72%. We

Table 5
Logistic regression of patients' first screening status for early stage (stages 0–1) diagnosis.

	Model 1			Model 2			
First screening status	Odds ratio	95% Confidence interval (Lower, Upper)	p-value	Frequency of screening before cancer diagnosis	Odds ratio	95% Confidence interval (Lower, Upper)	p-value
Confirmed cancer	1.00	(0.90, 1.11)	0.9632		1.00	(0.90, 1.11)	0.9720
Confirmed OPMD	1.99	(1.78, 2.22)	< 0.0001	1	1.89	(1.65, 2.16)	< 0.0001
				2	1.13	(0.92, 1.39)	0.2380
				3 or more	1.15	(0.85, 1.55)	0.3557
Confirmed non-OPMD	1.85	(1.59, 2.15)	< 0.0001	1	1.77	(1.46, 2.16)	< 0.0001
				2	0.95	(0.69, 1.31)	0.7440
				3 or more	1.68	(1.06, 2.66)	0.0269
Not confirmed	1.25	(1.10, 1.43)	0.0007	1	1.01	(0.85, 1.20)	0.8980
				2	1.38	(1.07, 1.78)	0.0135
				3 or more	2.76	(1.87, 4.07)	< 0.0001
Not referred	1.49	(1.38, 1.62)	< 0.0001	1	1.32	(1.19, 1.46)	< 0.0001
				2	1.18	(1.04, 1.34)	0.0121
				3 or more	1.67	(1.40, 1.99)	< 0.0001
No screening	1.00			no screening	1.00		

Also adjusted for age group, gender and year of diagnosis.

Table 6
Cox regression of patients' first screening status for mortality.

		All cause death			Oral cavity death		
Parameter		Hazard Ratio	95% Confidence interval (Lower, Upper)	p-value	Hazard Ratio	95% Confidence interval (Lower, Upper)	p-value
First screening status	Confirmed cancer	0.87	(0.81, 0.95)	0.0008	0.92	(0.84, 1.00)	0.0516
	Confirmed OPMD	0.71	(0.63, 0.78)	< 0.0001	0.72	(0.64, 0.81)	< 0.0001
	Confirmed non-OPMD	0.84	(0.73, 0.97)	0.0166	0.86	(0.73, 1.01)	0.0593
	Not confirmed[a]	0.87	(0.78, 0.97)	0.0112	0.85	(0.75, 0.97)	0.0128
	Not referred	0.87	(0.81, 0.93)	< 0.0001	0.84	(0.77, 0.90)	< 0.0001
	No screening	1.00			1.00		
Stage	0~1	1.00			1.00		
	2	1.74	(1.55, 1.94)	< 0.0001	2.04	(1.78, 2.34)	< 0.0001
	3	3.10	(2.76, 3.48)	< 0.0001	3.88	(3.38, 4.45)	< 0.0001
	4	6.71	(6.15, 7.31)	< 0.0001	9.00	(8.08, 10.03)	< 0.0001
	Not available	6.52	(5.72, 7.43)	< 0.0001	6.99	(5.94, 8.23)	< 0.0001
Age group	< 45	1.00			1.00		
	45 ~ 54	1.03	(0.95, 1.12)	0.4480	0.97	(0.89, 1.06)	0.5058
	55 ~ 64	1.11	(1.02, 1.20)	0.0170	0.99	(0.90, 1.09)	0.8470
	65+	2.00	(1.84, 2.18)	< 0.0001	1.78	(1.62, 1.96)	< 0.0001
Gender	Female	1.00			1.00		
	Male	1.25	(1.14, 1.37)	< 0.0001	1.17	(1.06, 1.30)	0.0029
Year of diagnosis	2012	1.00			1.00		
	2013	1.00	(0.93, 1.07)	0.9717	1.01	(0.93, 1.09)	0.8554
	2014	0.97	(0.90, 1.04)	0.3375	0.97	(0.90, 1.06)	0.5022
	2015	1.00	(0.92, 1.08)	0.9237	0.96	(0.88, 1.06)	0.4148

[a] Screened positive, but did not complete diagnosis confirmation.

found an 80% (5274/6609) rate of compliance among patients with prior screening records. Although in the past the effect of poor patient compliance to oral cancer screening program may not be clear [24], our results show that patients with a first screening status of not confirmed also have significantly better chance of early diagnosis (OR = 1.25, 95% CI = 1.10–1.43, p = 0.0007; stages 0–1: 31.3%) and mortality reduction (HR = 0.87, 95% CI = 0.78–0.97, p = 0.0112) compared to non-screening patients. In TOMS program, when patients did not complete their diagnosis confirmation, they would be remained on the continuing contact list until confirmation obtained. Sometimes they may choose to attend the next scheduled screening. If these patients continue to participate in subsequent routine screenings, their chance of being diagnosed at earlier stages performed a dose-response effect with increasing frequency of screenings. One additional screening is corresponding to 5.1% more in early-stage proportion and 1.38 times (95% CI = 1.07–1.78, p = 0.0135) of the chance being diagnosed at early stages. For two or more additional screenings, these statistics are 20.6% and 2.76 (95% CI = 1.87–4.07, p < 0.0001). These findings are consistent with Chuang et al. [7], which a higher repeated screening rate was expected to have a 28% (95% CI, 27%-30%) reduction of oral cancer mortality.

When the high-risk group could be identified from the cancer screening program, the detection and treatment of early stage cancers would significantly reduce mortality [25]. The screening intervention provides a protection effect for preventing malignant transformation in precancerous status [4,26]. The value of screening programs is therefore not only limited to the detection of oral cancer or OPMD. It is also possible to organize the concepts of cancer awareness and risk factor reduction into the implementation of the screening program in a way that is appropriate and acceptable to the targeted high-risk population [27,28]. The promotion of public awareness about oral cancer and integration into the public health delivery systems may increase the effectiveness of community-based screening programs to identify early-stage oral cancer [24]. In TOMS program, during oral visual inspections examiners would deliver a conversion on the risk of chewing and smoking habits. Participants would also be encouraged to attend betel

quid and tobacco cessation programs. The benefit of intervention was previously reported by Chuang et al. [7]. Our results show that the proportions of early stages are 31.3% for patients with incomplete comfirmation at screening and 35.3% for patients not referred at their first screening. These proportions of early stage diagnosis are all higher than for patients without any prior screenings (27.8%). Around two-thirds of these patients attend subsequent screenings. All of the cancer patients with a first screening status regardless of their compliance with confirmation have a significant survival benefit. It therefore seems possible that participating in the screening itself may increase awareness and translate into the better clinical effect of earlier diagnosis and reduced mortality.

The 2-year screening interval was determined by a health technology assessment conducted by Taiwan health officials. In TCR, there are still 19.1% of patients with negative screening results, which could be partially due to interval cancers. The median days of last screening to cancer diagnosis (Table 4) are from 154 to 294 days. A screening study in Japan also indicated new incidences of leukoplakia within a year [29]. There are possibilities that interval cancers could occur within the 2-year interval. Therefore, a risk-stratified approach may need to be evaluated according different probabilities of developing cancers.

This study has some limitations. The first is that it is a retrospective cohort study and some covariates, such as self-selection factors relating to screening behavior and detailed information about personal habits could not be considered because of their absence from the data collection. The second is the limited follow-up period included in this study, although the high-quality database from well-organized government projects should still provide very valuable evidence on the oral cancer screening program.

Our study shows that there is no obvious stage-shift when participants present to screening with cancers. Identifying a non-cancer disorder in the organized screening program with a subsequent follow-up strategy allows participants to have a better overall clinical outcome due to earlier detection compared with their non-screened counterparts.

Conflict of interest

None declared.

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