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Cost-effectiveness analysis of the oral cancer screening program in Taiwan

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ABSTRACT

Objectives: We assess the incremental cost-effectiveness ratio (ICER) of the oral cancer (OC) screening program in Taiwan.

Materials and methods: We interlinked the Cancer Registry, Mortality Registry, National Vital Statistics, reimbursement database of National Health Insurance, and the National Oral Cancer Screening database of Taiwan. A total of 40,092 pathologically verified OC patients were identified and followed during 2002–2014. After stratification by stages, lifetime survival curves were estimated by a rolling extrapolation algorithm to obtain life expectancy (LE), expected years of life lost (EYLL), and lifetime medical costs (LMC).

Results: The LE for stages I-IV were 19.5, 14.0, 11.9, and 7.7 life-years, respectively, while those of EYLL were 7.3, 12.2, 15.4, and 18.7 life-years, respectively. The LMC for stages I-IV were US$ 65,752, 60,086, 53,675, and 47,570, respectively. We assumed no life loss for stage 0 with LMC of US$ 5380 spent for the first year after diagnosis. During 2010–2013, 967 out of the 28,018 cases detected with abnormal oral pathology by screening were found to develop OC. The ICER of the screening program was US$ 28,516 per life-year saved, which could be improved to US$ 5579 per life-year saved if all cancers transformed from abnormal oral pathology were detected before stage I.

Conclusion: The ICER of the current OC screening program in Taiwan slightly exceeds 1 GDP (gross domestic product) per capita per life-year saved. Intensive follow-up and treatment for all patients with abnormal oral pathology would improve screening efficiency and effectiveness of prevention.

Introduction

Head and neck cancer is the sixth most common cancer worldwide and about 40% of these cases are diagnosed as oral cancer (OC) [1]. Many OC evolve from malignant transformations of oral potentially malignant disorders (OPMDs), such as squamous hyperplasia, hyperkeratosis, verrucous hyperplasia, submucous fibrosis, lichen planus, etc. The malignant transformation rates for OPMDs are different depending on histopathology, cellular dysplasia, ethnicity and personal lifestyle [2,3].

The prognosis of OC depends on its specific site and stage. The five-year overall survival rates of OC in Taiwan for stages I, II, III, and IV were 78.98%, 69.38%, 54.62%, and 36.17%, respectively [4]. These low survival rates may result from high incidences of locoregional recurrence and distant metastasis [5]. Multidisciplinary treatments are required for the survival of late stage or recurrent OC, which in turn lowers the quality of life and increases the financial burden of the Taiwan Health Insurance system. Therefore, early detection of OC and OPMDs by oral screening among high risk groups may shift the diagnosis of OC to early stages, and reduce mortality [6].

A large cluster-randomized controlled screening trial in Kerala, India, showed a significant reduction in mortality for male tobacco and/or alcohol users at 3-year intervals from 1996 to 2004 [7]. Based on Markov chain model analysis [8], Dedhia and his colleagues found a community-based oral screening program targeting high-risk males would dominate those without such a program. However, studies of

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oral screening from the United States did not show a similar result [9,10]. The inconsistency between these studies may be partially related to lead- or length-time bias and lack of technology to evaluate outcomes from a lifetime horizon [4,11].

In Taiwan, the Health Promotion Administration of the Ministry of Health and Welfare started a program of OC screening in 2004. It provides free oral mucosal examination every two years for Taiwan residents with a habit of smoking and/or betel quid chewing who are > 30 years old or aborigines > 18 years old. The screening is conducted through inspection and palpation by primary care physicians. People with positive results (including OPMDs, uncategorized oral diseases and suspicious OC) are referred to an oral maxillofacial surgeon or otolaryngologist for confirmatory diagnosis, including incisional biopsy.

Through interlinkages of real world databases, we intended to estimate cost-effectiveness considering both the lifetime horizon and malignant transformation of OPMDs and uncategorized oral pathology (UCOP). Namely, the aims of this study were to estimate the life expectancy (LE), expected years of life lost (EYLL), and lifetime medical costs (LMC) for patients with OC diagnosed by the screening program versus OC not diagnosed by screening to assess the incremental cost-effectiveness ratio (ICER) in Taiwan.

Materials and methods

The study was approved by the Institutional Review Board of National Cheng Kung University Hospital (IRB number: B-ER-104-103). We established an OC cohort through inter-linkages of national databases from the Taiwan Cancer Registry (TCR), National Health Insurance (NHI), and National Mortality Registry. From the cohort, we estimated LE, EYLL, LMC per case, and costs per life-year saved for OC. Through linkages of the TCR and OC Screening database, we identified OC cases who were and were not diagnosed by the screening program, as well as those previously detected with abnormal pathology in cancer screening but were later found with malignant transformation. Then, we analyzed the effect of stage shifting and ICER by screening. The whole process is summarized in Fig. 1.

Establishment of oral cancer (OC) cohort

Following the third edition of the International Classification of Diseases for Oncology (ICD-O-3), we included oral cavity cancers coded as C00.0-C06.9 and excluded malignant neoplasms of oropharynx (C01, C02.4, C05.1, and C05.2). The age groups were stratified into 0–49, 50–64, and ≧65 years old to be comparable with our previous study [4] for estimations of LE, EYLL and LMC. In total, we included 40,092 pathologically verified OC patients registered in the TCR from 2002 to 2014. Patients' gender, age at diagnosis and stage were obtained from the database. All data were first linked with the National Mortality Registry to determine if the patients were still alive by the end of 2014. All patients were classified by pathological staging based on the American Joint Committee on Cancer staging system. If the pathological stage was absent, the clinical stage was used.

By natural course, a person screened negative may develop oral cancer > 6 months later. And the current system requires healthcare providers to call those with positive results back for further diagnostic work-up within 3 months. The governmental policy also provides bonus incentives for screening providers, say, accomplishing > 85% confirmatory rate for medical center in addition to regular screening fees, which appeals to most providers. In general, the high (> 99%) enrollment rate of the NHI system in Taiwan provides high accessibility to healthcare services for all people, including dentistry and otolaryngology. Thus, we classified people with OC as diagnosed by screening only if they were diagnosed no later than 6 months after being screened positive to avoid confounding, which would underestimate the true effectiveness of screening. Whenever there was no previous record of screening or if the date of screening was more than 6 months prior to data collection, we defined such OC cases as diagnosed outside of the program.

Estimation of LE, EYLL and LMC of oral cancer (OC)

The LE of OC was calculated with the survival function estimated by an algorithm of rolling extrapolation, aided by external information of onset age-, sex-, and calendar year of diagnosis-matched referents for the cohort, described briefly as follows [11]. First, the Kaplan-Meier (KM) method was applied to estimate the survival curve for the OC cohort, on the basis of the observed data, to the end of follow-up. Second, survival data of a reference population matched with the OC cohort for onset age and sex were generated from the life tables of the general population of Taiwan in the corresponding year using a Monte-Carlo method. The complete survival curve of the matched referents was then obtained using the KM method. Third, the ratio between the two survival curves of the OC cohort and the reference population, denoted as W(t) was defined and further transformed into a logit scale to obtain a flattened curve, denoted as logit W(t). Fourth, a restricted cubic splines model was used to fit the logit W(t) during the observed period, from time zero to the last month of follow-up, for predicting logit W(t) one month ahead. The predicted value was treated as newly "observed" and the observed period was shifted one month ahead. A new restricted cubic splines model was fitted to the logit W(t) during the updated observed period and was used to generate predictions for the next month. The process was repeated step-by-step from the end of follow-up to end of life. Finally, the lifetime survival curve of the OC cohort was obtained from back transformation of logit W(t) and the lifetime survival curve of the matched referents. The area under the estimated lifetime survival curve was the LE estimate of the OC cohort. The EYLL of OC was estimated by subtracting the LE of the OC cohort from that of the age-, sex-, and calendar year of diagnosis-matched referents simulated from vital statistics of the OC cohort. The standard errors of LE and EYLL were obtained through a bootstrap method by conducting the extrapolation process with data simulated by repeated sampling with replacements from the real data set 100 times. The iSQoL2 software (http://sites.stat.sinica.edu.tw/isqol/) was used for the estimation.

Estimation of lifetime medical costs

From the reimbursement data of the Taiwan NHI, we obtained details on spending for all the OC cases between 2002 and 2013. In Taiwan, almost all OC cases were verified by pathology and could be registered as catastrophic illness and were waived from copayments. All direct medical costs were reimbursed by the NHI, including in- and outpatient expenditures, and those spent for diagnosis and treatments. The recorded costs of every case were summed up to calculate the monthly average healthcare expenditure of survivals after diagnosis to the end of follow-up. Transportation costs, payments to caregivers, nutritional costs and human capital loss were not available in this analysis. The mean cost function beyond the maximum follow-up time was estimated by a weighted average of the mean expenditures of patients in their final months prior to death. The weights were determined by the hazards which were converted from the extrapolated lifetime survival rates [11]. The estimated lifetime medical costs was calculated by summing up the products of monthly mean costs function and monthly survival rates estimated by the rolling extrapolation algorithm mentioned previously. We also used iSQoL2 software to calculate the lifetime costs.

Because the total number of OC patients at stage 0 was relatively small (n = 155) with a very high censored rate (83.2%) after 13 years of follow-up, as shown in Table 1, it would be inaccurate to extrapolate and estimate the lifetime survival function. Thus, we assumed that they would have no loss of life expectancy and that the medical costs caused

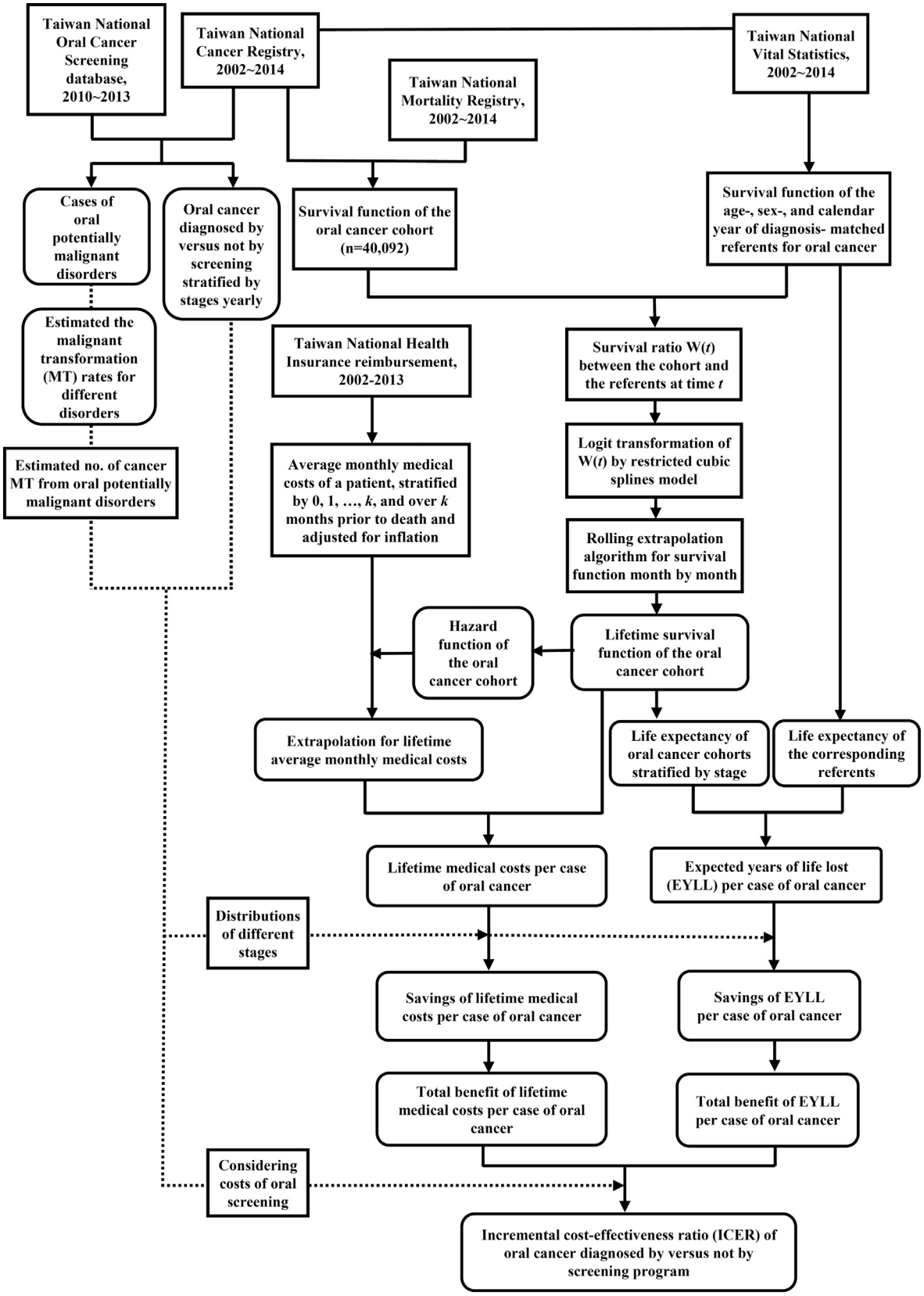

Fig. 1. Flow diagram of the inclusion of subjects and their relevant information for estimation.

Table 1
Estimated life expectancy (LE), expected years of life lost (EYLL) and lifetime medical costs (LMC) of oral cancer, stratified by gender, age and stage, follow-up during 2002–2014.

Stage	Gender	Age (years)	No. of cases	Age at diagnosis (mean ± S.D.)	Censored rate (%)	LE (SE) (years)	EYLL (SE) (years)	LMC [a] (SE) (USD)
0			155	55.4 ± 12.5	83.2	NA[b]	NA[b]	5380 (6978)[c]
I			12,157	53.8 ± 12	80.0	19.50 (1.23)	7.33 (1.23)	65,752 (3208)
	Male		10,733	53.2 ± 11.5	79.8	18.87 (1.25)	7.94 (1.25)	65,962 (3798)
	Female		1424	58.4 ± 14.7	82.0	19.92 (2.69)	6.89 (2.69)	NA[b]
		0–49	4548	41.9 ± 5.7	83.8	18.05 (0.93)	18.33 (0.93)	62,930 (2795)
		50–64	5315	56.1 ± 4.1	82.0	16.61 (1.03)	7.88 (1.03)	66,821 (3809)
		≧65	2294	72.2 ± 5.9	67.8	9.71 (0.54)	3.51 (0.54)	43,289 (2640)
II			8213	54.4 ± 12.4	69.6	13.96 (0.74)	12.24 (0.74)	60,086 (3516)
	Male		7462	53.6 ± 11.8	69.8	14.72 (1.01)	11.77 (1.01)	63,588 (3536)
	Female		751	62.5 ± 14.9	67.6	12.27 (1.66)	11.14 (1.66)	53,726 (5853)
		0–49	3022	42.1 ± 5.5	74.6	18.88 (1.57)	17.06 (1.57)	69,505 (4057)
		50–64	3482	56.2 ± 4.2	72.7	13.51 (0.61)	10.81 (0.61)	60,248 (2678)
		≧65	1709	72.7 ± 6.5	54.2	7.71 (0.36)	5.16 (0.36)	39,208 (2377)
III			4844	53 ± 11.9	56.7	11.93 (0.69)	15.36 (0.69)	53,675 (2228)
	Male		4461	52.2 ± 11.3	56.7	12.05 (0.95)	15.49 (0.95)	56,745 (2406)
	Female		383	61.3 ± 14.4	56.1	10.90 (2.09)	13.30 (2.09)	NA[b]
		0–49	2032	42.2 ± 5.2	60.7	13.47 (1.05)	22.29 (1.04)	59,238 (2770)
		50–64	2020	56 ± 4.1	59.2	11.27 (0.64)	13.11 (0.64)	57,253 (3321)
		≧65	792	72.6 ± 6.1	39.8	6.14 (0.42)	6.71 (0.42)	35,970 (2178)
IV			14,723	54.1 ± 12.1	38.3	7.71 (0.27)	18.66 (0.27)	47,570 (9 9 1)
	Male		13,538	53.4 ± 11.5	38.2	8.37 (0.47)	18.29 (0.47)	49,888 (1847)
	Female		1185	62.2 ± 15	39.2	8.06 (1.01)	15.55 (1.01)	40,635 (2906)
		0–49	5601	42.7 ± 5.1	39.2	8.89 (0.45)	26.58 (0.45)	50,984 (1702)
		50–64	6346	55.9 ± 4.1	42.2	7.71 (0.28)	16.74 (0.28)	48,738 (1563)
		≧65	2776	73.2 ± 6.6	27.4	3.89 (0.18)	8.65 (0.18)	31,579 (1004)

[a] Lifetime medical costs: in US dollars at exchange rate on 2013/12/31 (1 USD = 29.95 NTD) provided by the Central Bank at no discount rate paid by the National Insurance of Taiwan.
[b] NA: Estimations are not applicable due to small sample size and high censored rate.
[c] The lifetime medical costs of patients with stage 0 were replaced by the sum of health expenditure within one year after diagnosis.

by OC at stage 0 would be about the amount spent within one year after diagnosis.

Cost-effectiveness analysis of the oral cancer screening program

The effectiveness analysis of the OC screening program from 2010 to 2013 was conducted as follows: 1. Estimating the numbers and proportions of OC cases stratified by stage who were or were not diagnosed by the screening program. For OC cases diagnosed by screening, we also included those with abnormal oral screening biopsy (OPMDs and UCOP) and later found in the TCR (namely, malignantly transformed) during the 4 years of follow-up (i.e., 2010–2013). 2. Multiplying the proportion of OC cases in each stage diagnosed by screening versus those not diagnosed by screening with their corresponding LE, EYLL and LMC. 3. Summing up the stage-weighted EYLL and LMC for OC cases diagnosed by screening/not by screening separately and calculating the differences between them. The incremental health benefits and costs, or ICER, for the OC screening program was calculated. 4. Because many cases with OPMDs and UCOP were detected to have developed stage II-IV OC later on, indicating irregular surveillance, we conducted a sensitivity analysis, assuming all of them were intensively followed and detected at OC stage 0 or I.

Determination of malignant transformation rate (MTR) – from OPMDs or UCOP to oral cancer

We assumed that once the patients with abnormal oral biopsy findings in the oral screening database had OC records in the TCR, some of them had malignant transformations during the observation period. Therefore, we linked the OC screening database from 2010 to 2013 with the TCR to until the end of 2014 to obtain the malignant transformation rate and their corresponding stages. The abnormal oral screening biopsy was divided into OPMDs (squamous hyperplasia, hyperkeratosis, verrucous hyperplasia, submucosal fibrosis, lichen planus, mild dysplasia, moderate dysplasia and severe dysplasia) and other uncategorized oral pathology (UCOP). This information was utilized in the cost-effectiveness estimation to make it more comprehensive. As these cases had irregular surveillance, which could be improved through intensive monitoring, we assumed that they could be diagnosed at stage 0 or I in the sensitivity analysis.

Estimation of ICER of OC diagnosed versus not diagnosed by screening program

We multiplied the stage-specific EYLL and LMC of OC with the proportion of cases in each stage and summed up the overall results for OC diagnosed and not diagnosed by screening from 2010 to 2013, respectively. Then, the ICER was calculated as follows:

((LMC for estimated OC diagnosed by screening + Cost of screening)
− LMC for OC not diagnosed by screening)
/[−(EYLL for estimated OC diagnosed by screening
− EYLL for OC not diagnosed by screening)]

If the program could be improved so that every case with abnormal oral lesions (or, OPMDs and UCOP) could be intensively monitored, say, every 3–6 months, and the transformed malignant lesions could be diagnosed at either stage 0 or I, we could then re-evaluate the ICER under these two different conditions through sensitivity analysis. Since EYLL is the loss of life expectancy, which means the number of life-years lost that could possibly be saved, we added a minus sign in front of the number to differentiate it from conventional life expectancy.

Table 2
The pathology of oral biopsy from oral screening and oral cancer diagnosed and not diagnosed by oral screening, stratified by calendar year.

	2010	2011	2012	2013
Pathology of oral biopsy by oral screening (n(%))				
Squamous hyperplasia	1482(18.4)	2175(24.4)	2176(27.2)	2355(30.3)
Hyperkeratosis	1162(14.4)	1216(13.6)	987(12.3)	803(10.3)
Verrucous hyperplasia	21(0.3)	321(3.6)	384(4.8)	423(5.5)
Submucosal fibrosis	0(0.0)	33(0.4)	52(0.7)	31(0.4)
Lichen planus	0(0.0)	28(0.3)	24(0.3)	41(0.5)
Mild dysplasia	834(10.3)	909(10.2)	649(8.1)	683(8.8)
Moderate dysplasia	266(3.3)	259(2.9)	251(3.1)	361(4.7)
Severe dysplasia	125(1.6)	131(1.5)	99(1.2)	116(1.5)
Uncategorized oral pathology	3034(37.6)	2517(28.2)	2242(28.0)	1828(23.6)
Total	6924(1 0 0)	7589(1 0 0)	6864(1 0 0)	6641(1 0 0)
Oral cancer diagnosed by oral screening [a] *(n(%))*				
Stage 0	8(0.6)	13(0.9)	5(0.4)	6(0.5)
Stage I	417(33.5)	462(31.1)	382(29.9)	396(31.7)
Stage II	243(19.5)	309(20.8)	262(20.5)	267(21.3)
Stage III	151(12.1)	194(13.1)	154(12.1)	140(11.2)
Stage IV	425(34.2)	507(34.1)	474(37.1)	442(35.3)
Total	1244(1 0 0)	1485(1 0 0)	1277(1 0 0)	1251(1 0 0)
Oral cancer not diagnosed by oral screening [b] *(n(%))*				
Stage 0	15(0.5)	21(0.7)	21(0.7)	27(0.8)
Stage I	937(31.0)	975(32.8)	1076(34.5)	1077(33.6)
Stage II	614(20.3)	567(19.1)	623(20.0)	620(19.3)
Stage III	362(12.0)	327(11.0)	335(10.7)	322(10.0)
Stage IV	1095(36.2)	1083(36.4)	1065(34.1)	1160(36.2)
Total	3023(1 0 0)	2973(1 0 0)	3120(1 0 0)	3206(1 0 0)

[a] Oral cancer diagnosed by screening: The registered date of pathologically verified oral cancer in the Taiwan National Cancer Registry being less than 6 months post positive oral screening.

[b] Oral cancer not diagnosed by screening: The inclusion criteria are as follows: (i) The registered date of pathologically verified oral cancer in the Taiwan Cancer Registry being more than 6 months post positive oral screening. (ii) Negative oral screening result. (iii) No oral screening.

Results

LE, EYLL, and LMC of oral cancer (OC)

From 2002 to 2014, there were 40,092 cases diagnosed as OC with pathologic proof in the database of the TCR. More than 90% of OC patients were male. Compared to males, more females were diagnosed at early stages (0–II) and older ages, as summarized in Table 1. The age of diagnosis for stage 0, I, II, III, and IV were 55.4, 53.8, 54.4, 53, 54.1 years old, respectively. The proportion of patients in each stage for stage 0, I, II, III, and IV were 0.39%, 30.32%, 20.48%, 12.08%, and 36.73%, respectively. The proportions of early (51.19%) and late stage (48.81%) OC were almost equal. The LMC of patients with stage 0 was replaced by the sum of health expenditures within the first year after diagnosis. In general, the LMC for OC in late stages, was lower than those of early stages (except for stage 0), because the latter usually survived longer and required more cost.

Oral cancer diagnosed by oral screening versus not diagnosed by oral screening

In total, 5257 OC cases were diagnosed by oral screening and 12,322 OC cases were not diagnosed by oral screening from 2010 to 2013. The rate of OC diagnosed by screening was about 30%. The percentage of early stage (0–II) OC diagnosed by screening and not diagnosed by screening were 52.7% and 53.3%, respectively (Table 2). Tests of a linear trend were performed for each calendar year to determine if screening detected OCs would show a higher proportion of patients in early stages. But we found there was no such trend, indicating no obvious stage shifting during the four-year period.

Malignant transformation rates (MTR), durations and stages from different OPMDs and UCOP to oral cancer

More than twenty percent of oral screening biopsy results in the Taiwan OC Screening database were diagnosed as uncategorized oral pathology (UCOP). A decrement in the percentage of UCOP was noted from 2010 to 2013 but squamous hyperplasia increased from 18.4% to 30.3% (Table 2). Table 3 summarizes the MTR details for lesions diagnosed as OPMDs and UCOP. Severe dysplasia had the highest MTR (20.2%), followed by moderate dysplasia (9.4%), verrucous hyperplasia (8.2%) and mild dysplasia (4.3%). The MTR of UCOP was 2.9% and was higher than those of squamous hyperplasia (2.1%) and hyperkeratosis (1.9%). Only three cases of submucosal fibrosis or lichen planus had malignant transformation. OC cases who were previously detected as OPMDs or UCOP showed a higher proportion of malignant transformation in early stages (0–II) (n = 627, 65%). Compared with those in Table 2, there appears to be a mild stage shifting for these lesions.

Estimated savings of EYLL, LMC, and ICER for OC screening

Table 4 shows the average EYLL and LMC of OC per case diagnosed by screening versus not by screening for 2010–2013, stratified by stage distributions from OPMDs and UCOP malignant transformation. According to data collected from the current program, we found that the estimated EYLL of OC by screening would be 13.06 years, if the OC was transformed or developed from OPMDs and UCOP, weighted by their OC stage distribution. Alternatively, if these cases were followed intensively and diagnosed at stage 0 or I, then the EYLL would be 11.19 and 12.40 years, respectively. The estimated LMC of OC transformed from OPMDs and UCOP by screening under the current program would be US$ 56,599; if they were all diagnosed at stage 0 or I, then the LMC would be US$ 48,439, and US$ 57,690, respectively. The EYLL and LMC of OC not diagnosed by screening were 13.17 years and US$ 56,410. We have provided Supplementary Tables 1–5 to show the detailed calculations of how the above estimates were worked out. And the differences of EYLL and LMC between OC diagnosed by screening versus not diagnosed by screening, namely, ΔEYLL and ΔLMC per case of OC under different scenarios are summarized in Table 4.

Because a total of 4,298,056 persons were screened during 2010–2013, we included the additional costs of implementing the program (Table 4). The ICER of oral screening can be calculated by dividing the incremental costs by the incremental effectiveness of life-years saved. The ICER of OC screening for all cases to stage I would be US$ 5579 per life-year saved, while that of stage 0 would be cost-saving, or, gaining US$ 2516 per life-year saved. Namely, had all cases been detected as OPMD & UCOP and were carefully followed every 3–6 months, they would have been diagnosed at an earlier stage, or, stage I or 0 when malignant transformation occurred. If all of these OC cases transformed from previously diagnosed OPMD & UCOP were detected at stage I or 0, then the oral screening program would be much more cost-effective.

Discussion

Many previous studies have reported on the LE, EYLL and LMC for OC, but the cost-effectiveness of OC screening remained undetermined. This work, to our knowledge, is the first to estimate the cost-effectiveness of a physician-based oral cancer screening program. This study has the following strengths: First, the confirmation diagnoses of this national oral screening program were only performed by a maxillofacial surgeon or otolaryngologist, and each biopsy was followed by pathology validation [6]. Thus, the quality of oral screening is fully assured. Moreover, according to our national survey, there were about 2 million and 4 million people in Taiwan with a habit of betel quid chewing and cigarette smoking, respectively [12,13]. The screening database showed that 4,298,056 high risk people received OC screening

Table 3
Numbers (No.), durations, and rates of malignant transformation (MT) from oral potentially malignant disorders and uncategorized oral pathology to oral cancer during 2010–2013, stratified by pathology and stage.

	Squamous hyperplasia	Hyperkeratosis	Verrucous hyperplasia	Mild dysplasia	Moderate dysplasia	Severe dysplasia	Uncategorized oral pathology
No. MT*/Total No.	172/8188	79/4168	94/1149	132/3075	110/1137	97/471	280/9621
MT rate	2.1%	1.9%	8.2%	4.3%	9.4%	20.2%	2.9%
No. of MT, (MT duration, mean ± S.D., weeks)							
Stage							
0-I	72(48.4 ± 50.3)	26(44.1 ± 45.3)	36(23.2 ± 33.1)	66(46.6 ± 49.9)	40(35.4 ± 45.2)	42(20.5 ± 26.4)	112(54.9 ± 60.2)
II	46(37.2 ± 48.5)	20(83.8 ± 51.3)	25(15.4 ± 26.8)	22(44.1 ± 48.4)	27(31.0 ± 46.8)	21(24.4 ± 37.1)	72(33.2 ± 46.1)
III	15(50.4 ± 54.7)	12(70.6 ± 37.0)	16(32.5 ± 38.0)	14(72.4 ± 65.3)	9(56.1 ± 57.6)	9(45.4 ± 70.3)	30(59.4 ± 56.1)
IV	39(37.8 ± 43.6)	21(73.0 ± 57.8)	17(47.7 ± 45.9)	30(55.4 ± 54.6)	34(51.8 ± 51.4)	25(23.3 ± 36.9)	66(42.9 ± 55.8)

The No. of MT/Total No. of submucosal fibrosis and lichen planus is 3/209 and the MT rate is 1.4%.
* including No. of stage 0.

during 2010–2013, which indicates a high coverage rate [6,14]. Second, the diagnosis of OC is accurate because every new case in TCR must be verified by two pathologists (Table 2). Since all treatments for pathologically validated cancer can be waived from co-payment under the Taiwan NHI system, the direct medical costs are relatively comprehensive and accurate. Third, we abstracted a nation-wide OC cohort and followed them for 13 years, which is close to the average LE of 13.96 years for stage II OC and longer than those of stages III and IV (Table 1). Because our analysis is based on real world data over 13 years of follow-up, there is no need for model assumption [8]. Besides, the extrapolation method has been mathematically proven to be valid if there is a constant excess hazard near the end of follow-up [15], which corresponds to each stratified OC subcohort, and the resulting LEs would be accurate. Fourth, we applied the differences of EYLL between OC diagnosed by screening and not diagnosed by screening as health benefits potentially gained from the screening program. Because comparison of EYLL was adjusted for different age distributions and lead time biases, our ICER estimation would be more accurate than by simply comparing LE. Finally, we assumed a scenario of intensive surveillance that could detect malignant transformation at an early stage for different abnormal oral pathologies (namely, OPMD & UCOP, in Table 3). This exploration sheds light on improving the effectiveness of the oral screening program. Namely, close monitoring and careful management of OPMDs and UCOP can save more life years and medical costs, especially for those diagnosed at stage 0 (Table 4). We thus conclude that these estimates of LE, EYLL and LMC are relatively accurate, and more intensive follow-up and management of abnormal oral screening pathology would improve the cost-effectiveness of the oral screening program in Taiwan.

Table 1 shows that there were more than 5600 or 14% of young people (< 50 years old) diagnosed with stage IV OC during 2002–2014. Compared with those diagnosed at stage I, stage IV OC suffered from a shorter LE (=8.89 years) and a longer EYLL (=26.58 years). Since these young OC patients were usually the major bread winners of their families, they would encounter financial challenges. After multidisciplinary treatments for OC diagnosed in late stages, they would usually be disabled with difficulties in speech, swallowing and/or damage in cosmetic appearance, which frequently results in loss of jobs and/or creates needs for long-term care or even caregivers. Again, detecting and treating these patients as early as possible would reduce such socioeconomic burdens in Taiwan.

This study has the following limitations: First, we defined the criteria for oral cancer by screening as "the registered date of pathologically verified oral cancer being less than 6 months post a positive result from oral screening", which might result in some misclassifications. We tried to change the definition of OC diagnosed by screening to "less than 3 months", which showed almost the same distribution (data not shown) and did not change our conclusion. Second, the oral screening database does not record the exact site of biopsy. Thus, we were unable to verify if the OC arose from the same site as the abnormal pathology found from oral screening. Future studies are warranted to tackle this issue. Third, we only followed patients for up to 4 years to determine the malignant transformation rates (MTR) for OPMDs and UCOP which was shorter than previous studies [3,16]. Therefore, we might have underestimated the MTR and the cost-effectiveness of an intensive surveillance program for people with suspected oral pathology from screening. Fourth, we only calculated the reimbursement fees for screening visits, which were not split into costs for space and personnel, fees for performing biopsy and reading pathology, etc. Detailed considerations of these factors would increase the costs of OC screening and may reduce the ICER for oral screening. However, since these costs are also generally reimbursed in the diagnostic work-up of our NHI, they would be offset by regular clinic visits. Nonetheless, our results might not be directly applicable to other countries without universal coverage. Fifth, we did not consider the screening attendance rate and screening sensitivity for ICER calculation. Because the stage distributions of OC diagnosed by screening and not by screening are similar under the current program (Table 2), attendance rate for screening may not influence our results too much. However, if screening sensitivity can be improved so that more people with early stage OC can be detected by screening, namely, there is stage shifting for those who participated in screening, then the cost-effectiveness could be better. Finally, this study did not consider the risk factors of OC and the comorbidities of patients with abnormal oral screening pathologies, which may influence the malignant transformation rates and stage distribution of OC. Future studies exploring how these factors affect malignant changes and recalculations of related EYLL and LMC estimates would be useful to improve the accuracy of cost-effectiveness of screening programs and the control of oral cancer.

In conclusion, the estimated costs per EYLL gained by oral cancer screening among high-risk people in Taiwan would slightly exceed 1 GDP per capita per life-year saved. Intensive surveillance and management of patients screened with abnormal oral pathology are needed so that malignantly transformed oral cancer can be diagnosed as early as possible (especially at stage 0 or I) and would consequently save more life years and medical costs and increase the cost-effectiveness of screening programs. The same recommendation is also useful to all healthcare professionals in Taiwan, because taking such actions would help save the lives of patients with abnormal oral pathology and potential oral cancer.

Conflicts of interest

None declared.

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Table 4
Estimated savings of expected years of life lost (EYLL), lifetime medical costs (LMC) and incremental cost-effectiveness ratio (ICER, no. of dollars spent per life-year saved) for oral cancer (OC) by screening, stratified with estimated malignant transformation (MT) of oral potential malignant disorder (OPMD) and uncategorized oral pathology (UCOP) by different stage distributions, and summations for 2010–2013.

MT of OPMD & UCOP to OC at different stage(s)	OC diagnosed by screening/Case		OC not diagnosed by screening/Case		Estimated saving for an OC diagnosed by screening		Estimated total benefit by oral screening (n = 6224)		Adding costs of screening ($4.34/person, N = 4,298,056)	ICER of OC screening
	$EYLL_s$	LMC_s	$EYLL_{ns}$	LMC_{ns}	ΔEYLL	ΔLMC	$\Delta EYLL_t$	$\Delta LMC_t(\times 10^6)$	Overall costs	US$/life-year
Current program	13.06	56,599	13.17	56,410	−0.11	190	−695.7	1.18	19,837,118	28,516
All to Stage 0	11.19	48,439	13.17	56,410	−1.98	−7970	−12,304.2	−49.61	−30,950,899	(cost-saving)
All to Stage I	12.40	57,690	13.17	56,410	−0.77	1280	−4772.1	7.97	26,625,222	5579

1. Note: $\Delta EYLL = EYLL_s - EYLL_{ns}$, $\Delta LMC = LMC_s - LMC_{ns}$; the overall cost of the current screening program is $\Delta LMC \times 6224$ cases ($= \Delta LMC_t$) plus the additional costs of screening operation of $18,653,563($= 4.34/person $\times$ 4,298,056 persons), then the above figure was divided by the net overall health benefits of 695.7 life-years gained from screening ($\Delta EYLL_t = \Delta EYLL \times 6224$ cases of OC diagnosed by screening) to obtain the ICER for the current program. Had participants been detected with OPMD & UCOP and malignantly transformed at stage 0 or I, then their ΔEYLL, ΔLMC, $\Delta EYLL_t$ and ΔLMC_t, as well as ICER would have been re-calculated as the above table; namely, cost saving for stage 0 and US$ 5579 per life-year saved for stage I.
2. Lifetime medical costs (LMC): in US dollars at the exchange rate on 2013/12/31 (1 USD = 29.95 NTD) provided by the Central Bank at no discount rate paid by the National Insurance of Taiwan.
3. The calculations of EYLL and LMC of OC diagnosed and not diagnosed by screening stratified by calendar year were presented in details in supplementary tables.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2018.12.011.

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