Original Article

Population-Based Screening Program for Reducing Oral Cancer Mortality in 2,334,299 Taiwanese Cigarette Smokers and/or Betel Quid Chewers

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BACKGROUND: To reduce oral cancer mortality, an organized, population-based screening program for the early detection of oral premalignancy and oral cancer was designed for high-risk individuals with habits of betel quid chewing, cigarette smoking, or both. The objective of this report was to evaluate the long-term effectiveness of this program in reducing the incidence of advanced disease and deaths from oral cancer. **METHODS:** A nationwide, population-based screening program for oral cancer has been conducted in Taiwan since 2004. Residents aged ≥18 years with oral habits of cigarette smoking and/or betel quid chewing were invited. The standardized mortality ratio method was used to compare the observed numbers of advanced oral cancers and deaths from oral cancer among screening attendees with the expected numbers derived from mortality among nonattendees. An intention-to-treat analysis of the relative rate of reductions in advanced-stage oral cancers and oral cancer mortality also was conducted. **RESULTS:** The overall screening rate was 55.1%. The relative risk of death from oral cancer was 0.53 (95% confidence interval [CI], 0.51-0.56) as a result of screening compared with the expected risk of oral cancer deaths in the absence of screening. The corresponding relative risk was 0.74 (95% CI, 0.72-0.77) after adjusting for self-selection bias. The relative risk of advanced oral cancer for the screened group versus the nonscreened group was 0.62 (95% CI, 0.59-0.64), which increased to 0.79 (95% CI, 0.76-0.82) after adjustment for self-selection bias. **CONCLUSIONS:** An organized, population-based oral cancer screening program targeting more than 2 million Taiwanese cigarette smokers and/or betel quid chewers demonstrated the effectiveness of reducing stage III or IV oral cancers and oral cancer mortality. These evidence-based findings corroborate and support the screening strategy of oral visual inspection for the prevention of oral cancer among high-risk individuals in areas with a high incidence of oral cancer. ***Cancer*** **2017;123:1597-609.** © *2017 American Cancer Society.*

KEYWORDS: betel quid chewing, cigarette smoking, mortality, oral cancer, population-based screening.

INTRODUCTION

It has long been recognized that oral cancer is related to 3 established risk factors, including betel quid chewing, cigarette smoking, and alcohol drinking.[1-3] One previous study in Taiwan also demonstrated that cigarette smoking and betel quid chewing increased the risk for leukoplakia, and drinking alcohol increased the risk for malignant transformation of oral premalignancy (OPM).[4] Because cancer prevention is an important issue in the domain of public health, an effective screening program for oral cancer has been envisaged.[1,5] The efficacy of population-based screening for oral cancer offered

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to average-risk individuals aged ≥ 35 years was addressed in a cluster-randomized, controlled trial in India and demonstrated a 21% nonsignificant reduction in oral cancer mortality for a group of average-risk individuals, but a significant 34% reduction was observed when the analysis was limited to consumers of tobacco, or alcohol, or both.[6]

Although population-based screening for oral cancer was demonstrated in the Indian randomized, controlled trial targeting the general population,[6] several subsidiary issues were raised. The first issue pertains to whether and how such a population-based screening program can be feasibly and effectively applied to high-risk individuals with different oral habits, such as cigarette smoking and/or betel quid chewing, in other international regions. For example, the oral habits in Taiwan are completely different from those in India.[6] Can the efficacy of oral visual inspection limited to a subgroup analysis of high-risk individuals demonstrated in the Indian randomized, controlled trial be reproduced in a large, population-based screening program to confirm its applicability? This point is also of paramount important to resource allocation, because approximately 90% advanced oral cancers and deaths from advanced cancer occur among smokers and/or chewers based on several previous international studies.[4,6,7] Screening for these high-risk individuals would be economically efficient, because it would avoid the inefficient allocation of resources for screening low-risk individuals.

The second issue is the extent to which the early detection of OPM and oral cancer in a population-based oral cancer screening program offered to high-risk individuals would be effective in reducing the incidence of and mortality from oral cancer. Moreover, the yields of early detection of different types of OPM through population-based screening in high-risk individuals have been never formally reported. In addition, investigations have barely addressed whether and how the early detection and successful treatment of OPM would lead to a reduction in the incidence of oral cancer.

The third issue is that evaluating the effectiveness of reducing oral cancer incidence and mortality in high-risk individuals cannot be entirely based on the randomized, controlled trial design because of ethical concerns regarding the high risk for oral neoplasia. To our knowledge, how to evaluate the effectiveness of a screening program with oral visual inspection applied to high-risk individuals in the absence of a randomized, controlled trial design has never been studied using a large, organized, population-based screening program in a quantitative manner.

To maximize the benefit of screening given limited health care resources and to answer the issues raised above, we designed a nationwide, biennial screening program for the early detection of oral neoplasia targeting high-risk individuals with oral habits of cigarette smoking and/or betel quid chewing in Taiwan. Starting in 2004, we implemented a first round and 3 subsequent rounds of oral visual inspection by trained physicians and dentists and organized a referral service to have confirmatory diagnosis of oral neoplasia. We then followed this large, population-based, screened cohort to ascertain data over time until 2009. The first objective of the current study was to report the basic results from prevalent and subsequent screening on the detection of OPM and oral cancer according to demographic features and types of oral habits. We also evaluated the effectiveness of the screening program in reducing the incidence rate of overall and advanced oral cancer as well as the mortality rate from oral cancer between attendees and nonattendees with and without adjustment for self-selection bias related to the program's screening rate.

MATERIALS AND METHODS

Study Samples

Between 2004 and 2009, a total of 4,234,393 individuals aged ≥ 18 years from the National Nutrition and Health Survey in Taiwan,[8] including 3,691,721 men and 542,672 women with habits of cigarette smoking, or betel quid chewing, or both, were targeted as the underlying eligible population for oral cancer screening (Supporting Table 1; see online supporting information). The general population comprised 18,196,790 individuals aged ≥ 18 years, including 9,086,195 men and 9,105,235 women. The proportions of cigarette smoking or betel quid chewing in Taiwan are 33.59%, 50.74%, 38.48%, and 23.14% in men and 7.41%, 7.53%, 3.77%, and 2.37% in women for groups ages 18 to 29, 30 to 49, 50 to 69, and ≥70 years, respectively. Residents aged ≥ 18 years with oral habits of either cigarette smoking or betel quid chewing were invited to participate in the Taiwanese nationwide biennial screening program for oral neoplasia, including OPM and oral cancer. Those who were diagnosed with oral cancer before the study period were excluded. Three main modes of detection were used. Screen-detected cases were defined as oral cancers diagnosed at a prevalent or subsequent screening. Interval cancers were defined as those diagnosed within 2 years or those diagnosed beyond 2 years since the last negative

screening. Nonattendees were defined as individuals who never participated in the screening program.

With the linkage to the National Cancer Registry until the end of 2009, information on the results from screening, times of screens, detection modes, and stage of oral cancer were retrieved. Information on demographic characteristics and survival status of patients with oral cancer was retrieved from the National Death Registry using codes from the International Classification of Diseases, 9th Revision-Clinical Modification (codes 140-141, 143-146, and 148-149) and from the International Classification of Diseases, 10th Revision (codes C00-C06, C09-C10, C12-C14) for lip cancer (140 and C00, respectively), tongue cancer (141 and C01-C02, respectively), gingival cancer (143 and C03, respectively), floor of mouth cancer (144 and C04, respectively), palate cancer (C05), other parts of mouth cancer (145 and C06, respectively), oropharyngeal cancer (146 and C9-C10, respectively), hypopharyngeal cancer (148 and C12-C13, respectively), and unspecified pharyngeal cancer (149 and C14, respectively). The entire cohort was followed over time to ascertain deaths from oral cancer until the end of 2012. The median follow-up was approximately 4.5 years.

Data Collection

The process of the Taiwanese nationwide biennial screening program for oral neoplasia is illustrated in Figure 1. First, information on demographic characteristics and on either cigarette smoking or betel quid chewing was collected through a questionnaire by face-to-face interviews in the communities/hospitals. Because the purpose of the study was to assess asymptomatic oral cancers, we excluded individuals who had oral cancer diagnosed before they were invited to the screening program. Second, the eligible participants (participants aged $\geq$ 18 years) were scheduled to receive visual inspection of the oral cavity by trained dentists or physicians. Clinical diagnoses of oral leukoplakia, erythroleukoplakia, erythroplakia, oral submucous fibrosis, and verrucous hyperplasia were defined as OPM. In the third stage of the referral process, the screen-positive participants with OPM or suspected malignancy were referred to specialists in the hospitals for confirmatory pathologic examination. The staging of oral cancer was based on the American Joint Committee on Cancer staging system (seventh edition).[9] Finally, participants who screened negative were invited to the next screening periodically at 2-year interscreening intervals and were also followed to ascertain interval cancers through linkage of the screened cohort with the National Cancer Registry. Those nonparticipants who were diagnosed with OPM and oral cancers also were monitored to ascertain oral cancer in a similar manner. The survival of those who had screen-detected and clinically detected oral cancers was monitored as indicated above.

Statistical Analysis

Descriptive results on the positive screening rate, the rates of referral rate and detection, and positive predictive values (PPVs) are reported as percentages. Kaplan-Meier analysis was used to calculate the cumulative incidence rate of oral cancer and to plot survival curves for attendees versus nonattendees according to the mode of detection. Because our eligible screening participants were limited to cigarette smokers, betel quid chewers, or both, it would have been difficult to estimate the incidence and mortality rates of the corresponding nonattendees with these 2 oral habits had they attended the screening, because information on these habits was not available for the nonscreened group. The alternative was to calculate the expected oral cancers and oral cancer mortality among nonattendees with these habits based on previous findings that approximately 90% of oral cancers and deaths from oral cancer were attributed to cigarette smoking, or betel quid chewing, or both.[4] The external validity of this information was further supported by very similar results from 2 previous studies, including the 90% rate reported by both Sankaranarayanan et al[6] and Ko et al in another Taiwanese study.[7] The expected deaths from oral cancers among nonattendees were estimated by using empirical data on oral cancers from 1,900,094 nonattendees, but we borrowed this external information to limit deaths from oral cancer among nonattendees as much as possible to oral cancers derived from the screened group with these habits. The similar applications were used to calculate the expected oral cancers and advanced oral cancers when self-selection bias adjustment was made. The effectiveness in reducing advanced cancer (stage III and IV) and deaths from oral cancer in terms of the relative risk (RR) was then estimated by using the standardized incidence and mortality ratios of the observed value in the screened group to the expected value from the nonscreened group, as calculated above. The standardized incidence ratio was applied to calculate the RR of overall and advanced (stage III and IV), incident oral cancer. The standardized mortality ratio was applied to the RR of death from oral cancer. To achieve intention-to-treat principle that makes allowance for self-selection bias[10] resulting from different risks between the screened and nonscreened groups, the RRs of advanced oral cancer and of death from oral cancer were further weighted by the screening rate using the

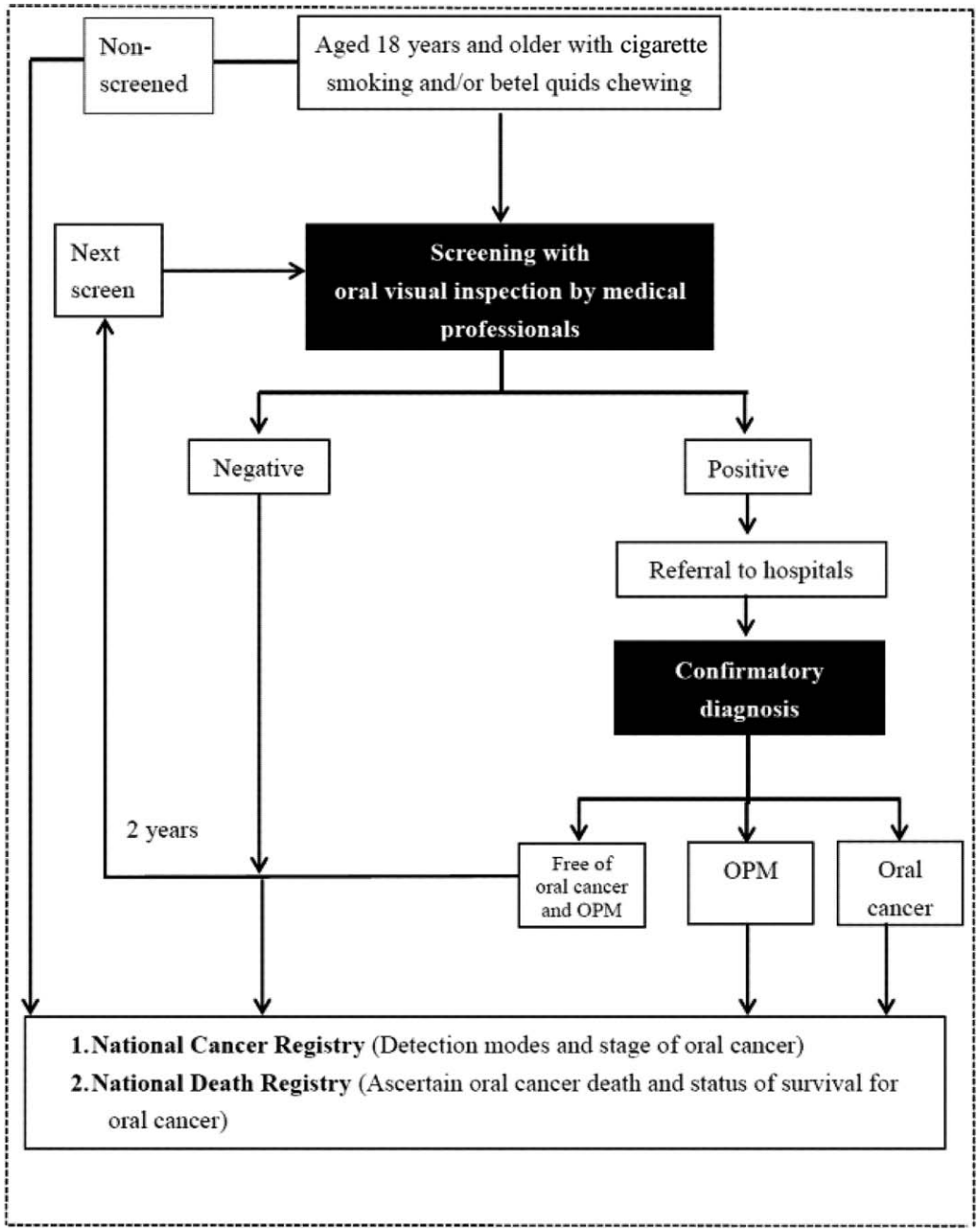

Figure 1. The workflow of the Taiwanese Nationwide Biennial Screening Program for Oral Cancer and Oral Premalignancy (OPM) is illustrated.

method previously described by Duffy et al and Tabar et al,[11,12] which takes the screening rate into account. We also computed the cumulative survival probability of oral cancer among screen-detected, interval cancers and the nonscreened group with the premise that 90% of deaths from oral cancer could be attributed to cigarette smoking and betel quid chewing. All statistical analyses were performed using SAS software (version 9.3; SAS Institute, Inc., Cary, NC).

RESULTS

Of 4,234,393 eligible individuals who were invited to the Taiwanese nationwide biennial screening program for oral neoplasia between 2004 and 2009, 2,334,299

TABLE 1. Basic Screening Findings of Taiwanese Nationwide Biennial Screening Program for Oral Neoplasia

Type of Screening by Sex and Age Group, y	Total No.	Screen Positive	Positive Rate, %	No. of Referrals	Referral Rate, %	Oral Premalignancy			Oral Cancer		
						No.	Detection Rate, ‰	PPV, %	No.	Detection Rate, ‰	PPV, %
First screening											
Men											
18-29	480,839	1521	0.3	1365	89.7	947	2	62.3	34	0.1	2.2
30-49	776,517	7847	1	6999	89.2	4835	6.2	61.6	1688	2.2	21.5
50-69	541,638	6083	1.1	5632	92.6	3644	6.7	59.9	1928	3.6	31.7
≥70	197,399	1242	0.6	1175	94.6	737	3.7	59.3	335	1.7	27
Women											
18-29	64,396	81	0.1	76	93.8	50	0.8	61.7	2	0[a]	2.5
30-49	126,917	369	0.3	324	87.8	209	1.6	56.6	27	0.2	7.3
50-69	112,247	710	0.6	671	94.5	459	4.1	64.6	63	0.6	8.9
≥70	34,346	263	0.8	252	95.8	170	4.9	64.6	33	1	12.5
Total	2,334,299	18,116	0.8	16,494	91.1	11,051	4.7	61	4110	1.8	22.7
Subsequent screening											
Men											
18-29	83,524	379	0.5	346	91.3	252	3	66.5	3	0[a]	0.8
30-49	198,661	2213	1.1	2001	90.4	1437	7.2	64.9	271	1.4	12.2
50-69	178,916	2086	1.2	1937	92.9	1342	7.5	64.3	399	2.2	19.1
≥70	89,603	612	0.7	594	97.1	393	4.4	64.2	86	1	14.1
Women											
18-29	4917	7	0.1	7	100	5	1	71.4	0	—	—
30-49	14,777	76	0.5	72	94.7	45	3	59.2	5	0.3	6.6
50-69	19,385	283	1.5	268	94.7	186	9.6	65.7	15	0.8	5.3
≥70	9320	169	1.8	166	98.2	122	13.1	72.2	12	1.3	7.1
Total	599,103	5825	1	5391	92.6	3782	6.3	64.9	791	1.3	13.6

Abbreviation: PPV, positive predictive value.
[a] Because decimals were rounded off to whole numbers, the actual detection rates of oral cancer were 0.04‰ in men ages 18 to 29 years in the subsequent screening and 0.03‰ in women ages 18 to 29 years at the first screening.

(55.1%) participated at the first screening and were screened at least once, 484,247 were screened at least twice, and 114,856 were screened at least 3 times, yielding a repeat rate (defined as being screened at least twice) of 20.7% (484,247 of 2,334,299 participants). The total number of subsequent screens for individuals who attended at least twice was 599,103 (484,247 + 114,856). Table 1 lists the results from basic screening according to screening mode, sex, and age group, consisting of positive screening rates, referral rates, detection rates, and PPVs for OPM and oral cancer. In total, 18,116 participants had a positive screening, and the overall screen-positive rate was 0.8% at the first screening. Among these 18,116 attendees, 16,494 who had suspicious lesions detected were referred for a confirmatory diagnosis, yielding a 91.1% overall referral rate. We identified OPM in 11,051 individuals and diagnosed oral cancer in 4110 individuals at the first screening, yielding overall detection rates of 4.7‰ and 1.8 ‰, respectively. The detection rate for OPM at the first screening among men increased from 2‰ for the group ages 18 to 29 years, to 6.2‰ for those ages 30 to 49 years, and to 6.7‰ for the group ages 50 to 69 years, and then declined to 3.7‰ for those aged ≥ 70 years. A similar age trend with smaller rates was observed among women. The detection rate for oral cancer among men increased from 0.1‰ for the group ages 18 to 29 years, to 2.2‰ for the group ages 30 to 49 years, and to 3.6‰ for group ages 50 to 69 years, and then declined to 1.7‰ for those aged ≥ 70 years. A similar age trend with smaller rates was observed among women. The PPVs of OPM ranged from 56.6% to 64.6% and did not differ significantly among age groups for either sex, whereas the corresponding PPVs for oral cancer had a statistically significant increase with advancing age ($P < .01$), and men had higher PPVs than women (by 2-fold to 4-fold) at age 30 years and older. Similar trends were noted for subsequent screens, but it is interesting to note that the positive screening rate was higher at subsequent screenings compared with the first screening (1% vs 0.8%), and the detection rate of OPM also was higher at subsequent screenings (6.3‰) than at the first screening (4.7‰). These findings were particularly remarkable for women aged ≥50 years. Conversely, the detection rate of oral cancer was higher at the first screening (1.8‰) than at subsequent screens (1.3‰).

The detection rate of OPM among men at the first screening increased from 2.3‰ for cigarette smoking alone, to 6.4‰ for betel quid chewing alone, and up to

TABLE 2. Basic Screening Findings by Different Oral Habits in Taiwanese Nationwide Biennial Screening Program for Oral Neoplasia

Type of Screening	Oral Habits: Cigarette Smoking	Oral Habits: Betel Quid Chewing	Participants	Screen Positive	Positive Rate, %	No. of Referrals	Referral Rate, %	Oral Premalignancy: No.	Oral Premalignancy: Detection Rate, ‰	Oral Premalignancy: PPV, %	Oral Cancer: No.	Oral Cancer: Detection Rate, ‰	Oral Cancer: PPV, %
First screening													
Men	Yes	No	924,145	3349	0.4	3157	94.3	2085	2.3	62.3	807	0.9	24.1
	No	Yes	118,195	1210	1	1136	93.9	753	6.4	62.2	291	2.5	24
	Yes	Yes	954,053	12,134	1.3	10,878	89.7	7325	7.7	60.4	2887	3	23.8
Women	Yes	No	218,937	482	0.2	452	93.8	295	1.3	61.2	34	0.2	7.1
	No	Yes	57,009	584	1	543	93	376	6.6	64.4	59	1	10.1
	Yes	Yes	61,960	357	0.6	328	91.9	217	3.5	60.8	32	0.5	9
Total			2,334,299	18,116	0.8	16,494	91.1	11,051	4.7	61	4110	1.8	22.7
Subsequent screening													
Men	Yes	No	208,681	965	0.5	927	96.1	632	3	65.5	156	0.7	16.2
	No	Yes	33,794	440	1.3	409	93	278	8.2	63.2	77	2.3	17.5
	Yes	Yes	308,229	3885	1.3	3542	91.2	2514	8.2	64.7	526	1.7	13.5
Women	Yes	No	19,883	42	0.2	41	97.6	31	1.6	73.8	1	0.1	2.4
	No	Yes	16,028	375	2.3	366	97.6	259	16.2	69.1	18	1.1	4.8
	Yes	Yes	12,488	118	0.9	106	89.8	68	5.4	57.6	13	1	11
Total			599,103	5825	1	5391	92.6	3782	6.3	64.9	791	1.3	13.6

Abbreviation: PPV, positive predictive value.

7.7‰ for having both oral habits (Table 2). The corresponding proportions for oral cancer among men were 0.9‰ for cigarette smoking alone, 2.5‰ for betel quid chewing alone, and up to 3‰ for having both oral habits. The detection rate of OPM among women increased from 1.3‰ for cigarette smoking alone, to 6.6‰ for betel quid chewing alone, and to 3.50‰ for having both oral habits. The corresponding proportions for oral cancer among women were 0.2‰ for cigarette smoking alone, 1.0‰ for betel quid chewing alone, and 0.5‰ for having both oral habits. The overall PPV for OPM was 61% and did not differ substantially between men and women or across types of oral habits. The overall PPV for oral cancer was 22.7%. Men had statistically significantly higher values than women ($P < .05$). Similar trends for the type of oral habit were noted for subsequent screenings. The detection rates of OPM, particularly among women with betel quid chewing alone, were higher at subsequent screenings than at the first screening; whereas the detection rates of oral cancer among women at subsequent screenings were not much different from those at the first screening. However, these findings should be interpreted with great caution, because oral cancers among women were rare at the subsequent screening.

The detection rates for OPM subtypes by sex and oral habit are provided in Table 3. The most frequently detected, commonly observed OPMs (not including the category "other," because these included too many subtypes with sparse numbers) was leukoplakia, followed by submucous fibrosis, verrucuous hyperplasia, and erythroplakia/erythroleukoplakia. Consistent with the results provided in Table 3, the detection rates were higher at the subsequent screening than at the first screening regardless of the OPM subtype, except for verrucuous hyperplasia. This phenomenon was particularly noted for women with a habit of betel chewing alone.

Figure 2 illustrates the cumulative incidence rate of oral cancer according to the 3 different types of oral habits. Participants who both smoked cigarettes and chewed betel quids were at increased risk for oral cancer compared with those who only smoked cigarettes (RR, 2.77; 95% confidence interval [CI], 2.58-2.98). Individuals who only chewed betel quids had a statistically significantly higher risk than those who only smoked cigarettes (RR, 2.37; 95% CI, 2.10-2.67). Note that smoking, compared with nonsmoking, also led to a 17% elevated risk (RR, 1.17; 95% CI, 1.05-1.31) for oral cancer among betel quid chewers.

In total, 8033 oral cancers were diagnosed during the study period among individuals who attended the

TABLE 3. Detection Rates of Subtypes of Oral Premalignancy by Different Oral Habits

Type of Screening	Oral Habits		Detection Rate[a]					
	Cigarette Smoking	Betel Quid Chewing	Submucous Fibrosis	Leukoplakia	Erythroplakia	Erythroleukoplakia	Verrucous Hyperplasia	Others[b]
First screening								
Men	Yes	No	20.2	75.6	2.5	1.5	7.8	117.9
	No	Yes	123.5	187.8	10.2	11.8	35.5	268.2
	Yes	Yes	146.8	301.3	10.2	12.3	41.9	255.2
Women	Yes	No	5.9	26.5	0.5	0.9	5	95.9
	No	Yes	94.7	193	8.8	1.8	22.8	338.5
	Yes	Yes	51.6	127.5	11.3	1.6	9.7	148.5
Total			78.5	173.2	6.2	6.4	23.3	185.8
Subsequent screening								
Men	Yes	No	32.6	114.5	2.4	2.4	5.3	145.7
	No	Yes	145	266.3	20.7	14.8	29.6	346.2
	Yes	Yes	166.4	330.6	15.2	17.8	32.1	253.4
Women	Yes	No	5	35.2	5	0	5	105.6
	No	Yes	287	617.7	31.2	18.7	62.4	599
	Yes	Yes	72.1	224.2	16	8	16	208.2
Total			114.5	247.4	11.2	11.5	22.2	224.5

[a] The detection rate is per 100,000, and the denominator is referred to Table 2.
[b] Others included lichen planus, hyperkeratosis, squamous hyperplasia, benign epithelial hyperplasia, papilloma, fibroepithelial polyp, and others.

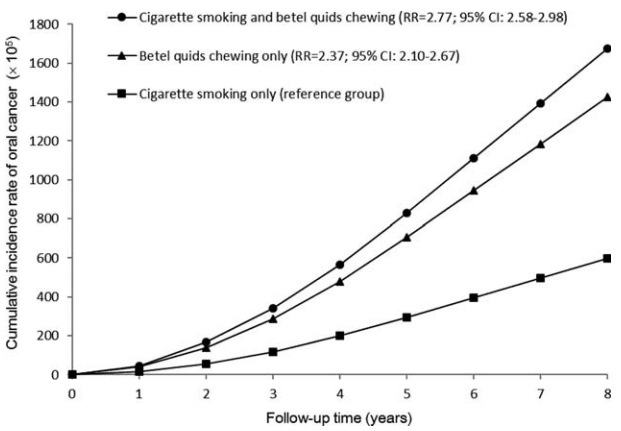

Figure 2. The cumulative incidence rate of oral cancer is illustrated among individuals with different oral habits. CI indicates confidence interval; RR, relative risk.

screening, consisting of 4110 detected at a prevalent screening, 791 detected at a subsequent screening, 1825 interval cancers detected at <2 years of follow-up (interscreening interval), and 1307 interval cancers detected at >2 years of follow-up. In all, 24,184 oral cancers were ascertained among 1,900,094 nonattendees. Table 4 indicates that, of 8033 screen-detected and interval cancers in the screened group, information on tumor stage was available for 87.4% of the participants, including 41 (0.6 %) with carcinoma in situ, 1837 (26.1%) with stage I disease, 1388 (19.8%) with stage II disease, 879 (12.5%) with stage III disease, and 2878 (41%) with stage IV disease (Table 4). The screened group had a higher proportion of early stage (ie, stage $\leq$ II) oral cancer than the nonscreened group (46.5% vs 39.6%; $P < .01$).

The overall incidence rate of oral cancer in the screened group (133.4 per 10^5) was statistically significantly lower than that in the nonscreened group (190.9 per 10^5). Applying the standardized incidence ratio yielded an RR of 0.69 (95% CI, 0.68-0.72) for oral cancer. After adjustment for self-selection bias resulting from nonscreening, the RR was 0.83 (95% CI, 0.81-0.86). Table 4 also indicates that the incidence rate in the screened group was lower for those with stage III and IV disease (62.4 per 10^5) compared with the nonscreened group (102.1 per 10^5), whereas the incidence rates of carcinoma in situ and stage I disease were not higher than those in the nonscreened group.

Table 5 details the risk of death from oral cancer using the standardized mortality ratio method, as described above (see Statistical Analysis), in the screened group versus the nonscreened group among men (RR, 0.57; 95% CI, 0.55-0.60) and women (RR, 0.17; 95% CI, 0.13-0.21). The corresponding rate for the overall group was 0.53 (95% CI, 0.51-0.56). After adjustment for self-selection bias, the RR of death from oral cancer was 0.77 (95% CI, 0.74-0.79) for men and 0.48 (95% CI, 0.44-0.53) for women. The corresponding rate for the overall group with both sexes combined was 0.74 (95% CI, 0.72-0.77). Comparisons of the cumulative mortality rate between the screened and nonscreened groups without and with adjustment for selection-bias are illustrated in Figure 3.

The RR of advanced oral cancer for the screened group versus the nonscreened group was 0.62 (95% CI,

TABLE 4. Stage Distribution of Oral Cancer Between the Screened and Nonscreened Groups[a]

Stage	Screened Group: Screen-Detected and Interval Cancer in Attendees		Nonscreened Group: Nonattendees	
	No. of Oral Cancers (%)	Incidence Rate, $\times 10^{-5}$	No. of Oral Cancers, (%)	Incidence Rate, $\times 10^{-5}$
0 (CIS)	41 (0.6)	0.7	129 (0.6)	1.0
I	1837 (26.1)	30.5	4508 (21.1)	35.6
II	1388 (19.8)	23.0	3821 (17.9)	30.2
III	879 (12.5)	14.6	2844 (13.3)	22.5
IV	2878 (41.0)	47.8	10,080 (47.1)	79.6
NK	1010	16.8	2802	22.1
Total	8033 (100)	133.4	24,184 (100)	190.9

Abbreviations: CIS, carcinoma in situ; NK, stage not known.
[a] Chi-square $P < .01$.

TABLE 5. The Effectiveness of Reducing Advanced Disease (Stage ≥ III) and Deaths From Oral Cancer in the Taiwanese Nationwide Biennial Screening Program for Oral Cancer

Sex	Total No. Eligible (Screening Rate, %)	No. With Stage ≥ III/No. of Deaths From Oral Cancer		Relative Risk [95% CI] Adjusted for Self-Selection Bias			
				No		Yes	
		Screened Group: Attendees	Expected Outcome Based on the Nonscreened Group: Nonattendees	Stage ≥ III	Deaths	Stage ≥ III	Deaths
Men	3,691,721 (54.1)	3645/2611	5443/4559	0.67 [0.64-0.70]	0.57 [0.55-0.60]	0.82 [0.79-0.86]	0.77 [0.74-0.79]
Women	542,672 (62.3)	112/88	626/521	0.18 [0.15-0.22]	0.17 [0.13-0.21]	0.49 [0.40-0.60]	0.48 [0.44-0.53]
Total	4,234,393 (55.1)	3757/2699	6069/5080	0.62 [0.59-0.64]	0.53 [0.51-0.56]	0.79 [0.76-0.82]	0.74 [0.72-0.77]

Abbreviation: CI, confidence interval.

0.59-0.64). After adjustment for self-selection bias, the RR of developing advanced oral cancer was 0.79 (95% CI, 0.76-0.82). In survival analyses, the unadjusted hazard ratios of death from oral cancer were 0.88 (95% CI, 0.84-0.92) for the screened group versus the nonscreened group, 0.87 (95% CI, 0.83-0.92) for the screen-detected group versus the nonscreened group, and 0.89 (95% CI, 0.84-0.95) for the interval cancer group versus the nonscreened group (Fig. 4). The results from multivariate survival analysis adjusting for explanatory variables, including age, sex, and tumor stage, are provided in Supporting Table 2 (see online supporting information). The adjusted hazard ratio increased from 0.88 (95% CI, 0.84-0.92) to 0.96 (95% CI, 0.91-1.01) for the screened group versus nonscreened group. Similar findings were noted for the screen-detected group versus the nonscreened group and for the interval cancer group versus the nonscreened group. This clearly demonstrates that stage shift as a result of early detection through screening accounts for the improvements in survival.

Although the difference in survival between the screened and nonscreened groups was not substantial, as expected, the observed 26% reduction in mortality described above was still consistent with the finding of a survival benefit, because mortality reduction is a function of reductions in both oral cancer incidence and case fatality (improved survival). The RR of 0.74 estimated for oral cancer mortality in Table 5 was close to the 0.73 rate calculated by the product of 0.83 (95% CI, 0.81-0.86) for the risk of incident oral cancer and 0.88 (95% CI,0.84-0.92) for the risk of death from oral cancer between the screened and nonscreened groups. These results strongly suggest that the 26% mortality reduction can be attributed in part to an improvement in survival and in part to a reduction in the incidence of oral cancer.

DISCUSSION

This study makes several novel contributions to an organized, population-based screening program for oral neoplasia. To our knowledge, it is the largest population-based, organized screening program for OPM and oral cancer to date among individuals with the habit of cigarette smoking or betel quid chewing (or both) to demonstrate whether the efficacy of oral visual inspection used in

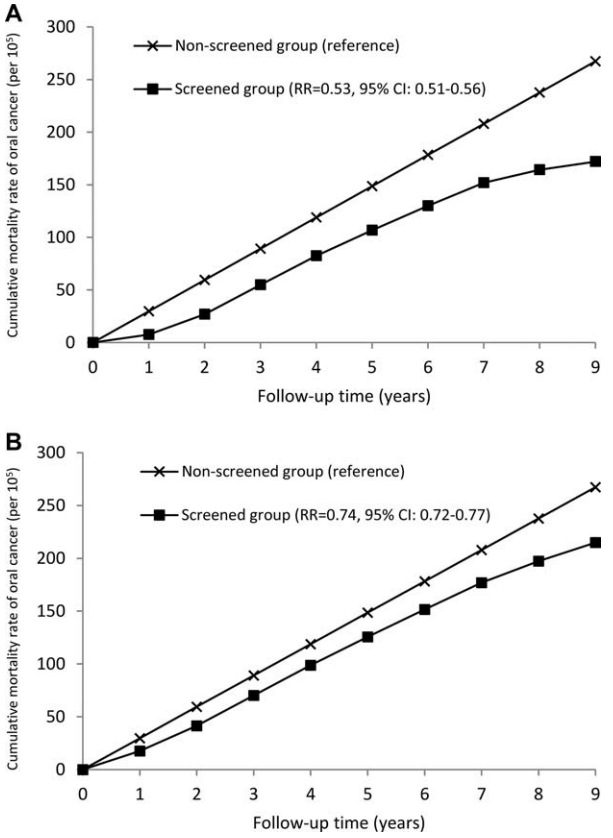

Figure 3. The cumulative mortality rate of oral cancer is illustrated in the current cohort (A) without self-selection bias adjustment and (B) with self-selection bias adjustment. CI indicates confidence interval; RR, relative risk.

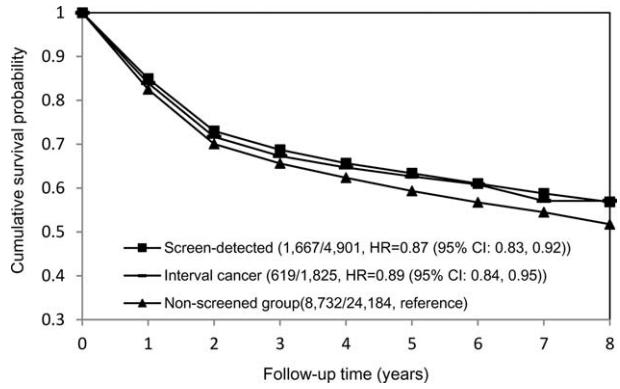

Figure 4. The cumulative probability of survival with oral cancer is illustrated for the screen-detected, interval cancer, and nonscreened groups. CI indicates confidence interval; HR, hazard ratio.

the Indian randomized trials (which were designed for an average-risk population) in reducing oral cancer mortality can be reproduced when applied to high-risk individuals (users of tobacco, or betel quids, or both) in Taiwan, where the types of oral habits differ from those in India. The results support the paradigm of evidence-based medicine in the prevention of oral cancer incidence and mortality that extends the efficacy of oral visual inspection during an era in which we are moving from a trial phase to a screening service phase.

The second major contribution of this study is that the reported yields from early detection include not only oral cancer but also different subtypes of OPM, as described above (see Results) and in Table 3. Providing information about OPM is a very important part of evaluating the impact of reducing oral cancer if oral malignant transformation through OPM is to be arrested. This is supported by the reduction in overall incidence observed in the screened group compared with the nonscreened group after adjusting for self-selection bias, although the follow-up is still short. Evaluating the effectiveness of reducing the incidence of advanced oral cancer is also important in explaining the reduction in oral cancer mortality. The consistent reductions in advanced-stage (stage $\geq$ III) oral cancers and deaths from oral cancer as a result of screening support the importance of early detection.

The third contribution of this study is that it provides unbiased estimates of the effectiveness of a population-based, organized screening service for high-risk individuals through oral visual inspection administered by medical professionals when a randomized, controlled study cannot be conducted on the grounds of ethical concerns over high-risk individuals. An effective screening program for oral cancer plays an important role in oral cancer prevention and mortality, particularly when the incidence and mortality rates have been rising worldwide.[13] The cluster-randomized, controlled trial using oral visual inspection designed for an average-risk population for the Indian trial was conducted in 1996 to demonstrate a nonsignificant 22% reduction in mortality, but a significant 34% reduction was reported after 9 years of follow-up when the subgroup analysis was limited to users of tobacco, or alcohol, or both.[6] However, the statistically significant reduction was observed only among men, and not among women, because of insufficient statistical power. A persistent 24% reduction (95% CI, 3%-40%) in oral cancer mortality was noted in this high-risk group after 15 years of follow-up.[14]

To demonstrate the applicability of oral visual inspection to high-risk individuals in Taiwan, a large, population-based, organized screening service program was instituted immediately after the results from this trial

has been published. We demonstrated a significant reduction (26%) in oral cancer mortality at an average of 4.5 years of follow-up after adjustment for self-selection bias attributed to 45% of nonattendees, indicating that the results are in line with the intention-to-treat analysis applied to the randomized, controlled trial. Our findings were consistent with those reported from the Indian randomized, controlled trial limited to high-risk individuals. However, in our trial, the efficacy of oral visual inspection was statistically significant for both men and women, in contrast to the differing sex-specific results reported from the Indian randomized, controlled trial. This difference suggests that the nonsignificant 22% reduction in oral cancer mortality among women reported in the Indian trial was caused by insufficient statistical power. The current findings corroborate the reproducible efficacy and feasibility of oral visual inspection demonstrated in the randomized, controlled trial.

In addition to demonstrating a reduction in oral cancer mortality, the evaluation of effectiveness in reducing advanced oral cancer is also very important for explaining the reduction. A Cochrane review in 2013[15] conducted by Sankaranarayanan[14] concluded that there was a statistically significant 19% reduction in the number of individuals diagnosed with stage III or worse oral cancer in the screening group (RR, 0.81; 95% CI, 0.70-0.93). Our study also confirmed this finding, with a lower incidence rate of advanced oral cancer (stage III or IV) and a 21% reduction in advanced (stage III or IV) oral cancer in the screened group compared with the nonscreened group. The reduction in advanced oral cancer in the screened group also suggests a stage shift in improved survival for the screened group in this nationwide Taiwanese biennial screening program. The survival rates were approximately 13% higher for screen-detected oral cancers and 11% higher for interval-detected cancers than for clinically detected cancers from the nonscreened group. The benefit of screen-detected oral cancer was attributed to early detection, whereas the improvement in survival for interval cancers may have been because of the awareness of early detection after screening uptake. This may be explained by a stage shift, because the adjusted hazard ratio for the screened group versus the nonscreened group increased from 0.88 to 0.96 after adjustment for age, sex, and tumor stage.

It also should be noted that this difference in survival as a result of early detection may not be greater than expected, because screening can lead to tumor downstaging but does not necessarily reflect an actual survival benefit, in part because 1) follow-up may not be longer, and 2) a delay in treatment resulting from poor compliance by patients with treatment protocols and medical regimes also may affect survival. This is particularly possible for patients with oral cancer in Taiwan, because the majority have low socioeconomic status, which may result in poor survival because of poor accessibility, as demonstrated in a previous study.[16] This poor compliance has improved in parallel with introduction of the screening program because of enhanced awareness in those who attend (the survival of patients with interval-detected cancer provides good evidence), although there is still room for improvement in patient education on adherence to medical regimes. This indicates that an even greater reduction in mortality would be expected if a substantial survival difference between the screened and nonscreened groups can be achieved through long-term follow-up or improvements in patient compliance behavior among those with early detected oral cancer who have low socioeconomic status.

Another innovative finding from this study is the demonstration of a significant 17% reduction in the incidence of overall oral cancer after adjusting for self-selection bias. To our knowledge, such a statistically significant finding has been never reported. The reduction in oral cancer incidence is mainly because malignant transformation is prevented through the early detection and treatment of OPMs that are detected by oral visual inspection by medical professionals in the program. Given a shorter follow-up, the prevention of such OPMs may consist mainly of verrucous hyperplasia, erythroplakia, erythroleukoplakia, and submucous fibrosis, because most of these have a short dwelling time compared with the majority of leukoplakias, which have an approximately 10-year dwelling time.

With regard to screening performance, there is a lack reporting on the sensitivity and specificity of oral visual inspection applied to population-based, organized screening, because it is impossible to have a confirmatory diagnosis in screen-negative individuals to enable an estimate of the incidence of false-negative results in such a large pool. A comparison of screening performance can be based only on the estimated PPV, which is a combination of prevalence, the detection rate, and the false-positive rate. An earlier systemic review by Patton demonstrated that the PPV for screening program ranged from 58% to 87%, depending on the prevalence of oral cancer in the underlying screened population.[17,18] The diagnostic accuracy of oral visual examination as a screening test in a primary settings, as reviewed by Walsh et al,[18] indicated that PPVs ranged from 31% to 86%, and negative predictive values ranged from 96% to 99%. Nagao et al reported the performance of a screening in the Japanese population by

the dentists, with an attendance rate of 68%, a compliance rate 68%, and a 78% PPV.[19] Our findings on the PPVs were not substantially different from those reported in previous studies. In our study, the PPV for OPM ranged from 57% to 65%, with an average of 61%, and did not vary significantly by sex, age, or types of oral habits. The average referral rate in our study was 91.05% and also did not vary by sex, age, or types of oral habits. The previous community-based, randomized, controlled trial in Taiwan also reported a 91% compliance rate and a 53% PPV, both of which were similar to the values in our current study.[20] Because health-behavior consciousness, compliance rates, and medical barriers vary from country to country, all of which may have an impact on the effectiveness of screening, the direct comparisons are limited.

It is interesting to note that detection rates of OPM were higher at subsequent screenings than at the first screening, whereas the opposite findings for invasive oral cancer were noted. Two possibilities may account for such findings. The first pertains to selection bias. Participants who attend repeated screening may have a higher risk for OPM than those who do not attend repeated screenings. This phenomenon could be observed in our study among women aged $\geq$50 years who had the habit of betel chewing alone. The second possibility is that the detectability of OPM by oral visual inspection was lower than that for invasive oral cancer. A missed OPM at the first screening would be picked up at the second screening. If this is true, then there are 2 solutions to the issue of detection rates: shortening the interscreening interval and improving the detectability of OPM. Because the dwelling time of OPM is sufficiently long (approximately 10 years), it may not be necessary to shorten the 2-year interscreening interval if the target is the early detection of oral cancer. Many new technologies may be developed for improving the detectability of OPM, although they may be limited to diagnosis and not screening, because still may be too expensive.

Regarding detectability by oral visual inspection, detection methods may vary from study to study. In the Indian trial, the detection method was based on trained health workers, whereas our study was based on medical professionals for visual inspection, including dentists and available physicians (including otolaryngologists) of all specialties after training to increase the provision of manpower. We did not collect details on all medical specialists. Therefore, we stratified 2 types of medical professionals who conducted visual inspections: dentists and physicians. The detection rate of OPM inspected by dentists was slightly higher than that by physicians (5.35‰ vs 4.39‰). A similar finding was noted for oral cancer (2.70‰ vs 1.79‰). Because of the large sample size, such differences were statistically significant ($P < .01$). The difference would be reduced by further standard training in the ongoing project.

Because different detection methods were used, it would be very interesting to estimate the sensitivity and specificity of oral visual inspection in such a large, population-based, organized screening program, although they cannot be directly calculated, as mentioned above. However, both estimates could be achieved by following interval cancers obtained from the cancer registry if the follow-up is sufficiently long. On the basis of the available follow-up information about interval cancers, the estimates of sensitivity and specificity were 88.29% and 99.47%, respectively. These estimates suggest that different detection methods used by various types of medical professionals may not have a substantial influence on the early detection of oral cancer.

Because our target population is mainly based on high-risk individuals, it also would be interesting to provide information about the extra medical costs required for detecting lesions and the reductions in advanced oral cancer incidence and mortality. By using a simple comparison method, the cost (in US dollars) for the first round of screening was \$2840 (2,334,299 $\times$ \$5/4110) per cancer detected and \$1056 (2,334,299 $\times$ \$5/11,051) per OPM detected. The cost of screening was \$1273 for 1 stage III or IV oral cancer averted and \$20,284 for 1 oral cancer death averted. Compared with other screening programs, such as those for breast cancer, these cost estimates seem lower. Such information is very valuable for health decision makers when resources are limited. However, because this is a population-based, organized screening program, it had better consider a comprehensive cost-effectiveness analysis. This was beyond the scope of the current study and will be the subject of ongoing research.

The current screening program has some limitations. One of its limitations is that the repeated screening rate was low. A higher repeated screening rate would be expected to enhance the reduction of oral cancer mortality to greater 28% (95% CI, 27%-30%); however, the repeated screening rate in our study was only 21%. We note that an 81% reduction (95% CI, 69%-89%) in oral cancer mortality was reported in an Indian randomized, controlled trial among a high-risk group of individuals who completed 4 rounds of screens after 15 years of follow-up.[14] The lower repeated rate may explain why our effectiveness in reducing oral cancer mortality using oral visual inspection by medical professionals was only slightly higher (by 6%) than that reported in the Indian

randomized, controlled trial using dental inspection by trained health workers, because their repeated screening rate was at least twice as high (55%) as ours.

The second limitation is that although a 17% reduction in incident oral cancer was demonstrated, the magnitude of effectiveness may have been underestimated because of a shorter follow-up. Because the average dwelling time for OPM is approximately 10 years, longer follow-up is required to validate the effectiveness of reducing the incidence of oral cancer in the future.

In conclusion, a population-based oral cancer screening program targeting Taiwanese cigarette smokers, or betel quid chewers, or both led to a 21% reduction in stage III or IV oral cancer diagnoses and a 26% reduction in oral cancer mortality and contributed both to a reduction in the incidence of oral cancer and to improved survival with a stage shift when adjusting for a 45% nonscreening rate. The implementation of an oral visual inspection screening strategy in high-risk individuals in countries with a high incidence of oral cancer plays an important role in the prevention of oral cancer.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Shu-Lin Chuang: Conceptualization, study design, supervision of draft preparation, data integrity, data acquisition, epidemiological and basic statistical analysis, in-depth statistical analysis on self-selection bias adjustment, writing–original draft, technical editing for draft, writing–critical review and revision, and final approval for publication. **William Wang-Yu Su**: Conceptualization, study design, supervision of draft preparation, data integrity, data acquisition, epidemiological and basic statistical analysis, writing–original draft, technical editing for draft, writing–critical revision for intellectual content, auditing clinical procedures, clinical interpretation of findings, and final approval for publication. **Sam Li-Sheng Chen**: Data acquisition, epidemiological and basic statistical analysis, in-depth statistical analysis on self-selection bias adjustment, writing–original draft, technical editing for draft, writing–critical revision for intellectual content, and final approval for publication. **Amy Ming-Fang Yen**: Data acquisition, epidemiological and basic statistical analysis, in-depth statistical analysis on self-selection bias adjustment, writing–critical revision for intellectual content, and final approval for publication. **Cheng-Ping Wang**: Writing–critical revision for intellectual content, auditing clinical procedures, clinical interpretation of findings, and final approval for publication. **Jean Ching-Yuan Fann**: Data acquisition, epidemiological and basic statistical analysis, writing–critical revision for intellectual content, and final approval for publication. **Sherry Yueh-Hsia Chiu**: Data acquisition, epidemiological and basic statistical analysis, writing–critical revision for intellectual content, and final approval for publication. **Yi-Chia Lee**: Writing–critical revision for intellectual content, auditing clinical procedures, clinical interpretation of findings, and final approval for publication. **Han-Mo Chiu**: Writing–critical revision for intellectual content, auditing clinical procedures, clinical interpretation of findings, and final approval for publication. **Dun-Cheng Chang**: Writing–critical revision for intellectual content and final approval for publication. **Yann-Yuh Jou**: Writing–critical revision for intellectual content; administrative, technical, or material support; and final approval for publication. **Chien-Yuan Wu**: Writing–critical review and revision; administrative, technical, or material support; and final approval for publication. **Hsiu-Hsi Chen**: Conceptualization, study design, supervision of draft preparation, data integrity, writing–original draft, technical editing for draft, writing–critical revision for intellectual content, writing–final review, study supervision, and final approval for publication. **Mu-Kuan Chen**: Conceptualization, study design, supervision of draft preparation, data integrity, writing–original draft, technical editing for draft, writing–final review, study supervision, and final approval for publication. **Shu-Ti Chiou**: Conceptualization; study design; supervision of draft preparation; data integrity; writing–original draft; technical editing for draft; writing–critical revision for intellectual content; administrative, technical, or material support; writing–final review; study supervision; and final approval for publication.

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