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## ABSTRACT

Early detection of oral premalignant lesions (OPMLs) by visual inspection with toluidine blue has not been addressed. We conducted a community-based randomized controlled trial to assess whether using toluidine blue as an adjunctive tool for visual screening had a higher detection rate of OPMLs and could further reduce the incidence of oral cancer. In 2000, in Keelung, we randomly assigned a total of 7975 individuals, aged 15 years or older and with high-risk oral habits, to either the toluidine-blue-screened (TBS) group or the visual screening group. Results showed 5% more oral premalignant lesions and 79% more oral submucous fibrosis detected in the TBS group than in the control group. After a five-year follow-up ascertaining oral cancer development through linkage to the National Cancer Registry, the incidence rate in the TBS group ( $28.0 \times 10^{-5}$ ) was non-significantly 21% lower than that in the control group ( $35.4 \times 10^{-5}$ ).

**KEY WORDS:** oral cancer, oral premalignant and malignant lesions, screening, toluidine blue, randomized controlled trial.

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# A Community-based RCT for Oral Cancer Screening with Toluidine Blue

## INTRODUCTION

The incidence of oral cancer has risen gradually over the past 40 years, and, since 1992, it has ranked as the seventh most common malignancy in Taiwan (Yang *et al.*, 2005). Thus, early detection of asymptomatic oral premalignant lesions (OPMLs), including oral submucous fibrosis (OSF), homogeneous leukoplakia, non-homogeneous leukoplakia, and erythroplakia, is imperative before their transformation into malignancies. It has been demonstrated (Sankaranarayanan *et al.*, 2000, 2005; Ramadas *et al.*, 2003) that proper visual screening could reduce the incidence of oral cancer.

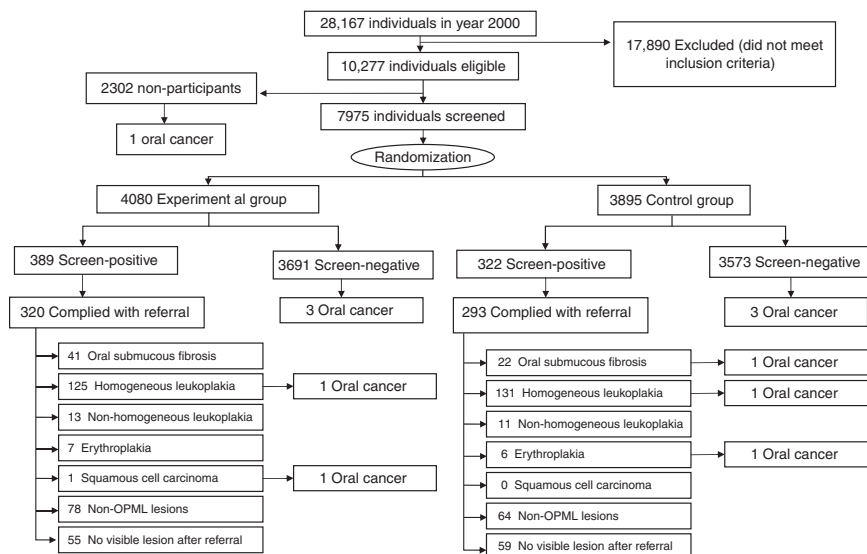
Since the 1980s, toluidine blue dye has been known to stain OPMLs and malignant lesions preferentially (Mashberg, 1980, 1981, 1984; Silverman *et al.*, 1984; Silverman and Migliorati, 1992; Martin *et al.*, 1998). Currently, it is widely used as an adjunctive tool for oral visual inspection, with a reported sensitivity of around 93.5-97.8%, a specificity of around 73.3-92.9% (Rosenberg and Cretin, 1989; Patton, 2003), and no false negativity for malignancies. However, few studies have examined whether adjunctive staining by toluidine blue contributes to enhancing the detection rates of visual screening for OPMLs. Thus, we conducted a community-based randomized controlled trial among individuals with high-risk oral habits to evaluate whether the use of toluidine blue as an adjunctive tool for visual screening results in a higher yield of OPML detection that, in turn, may lead to a reduction in oral cancer incidence.

## MATERIALS & METHODS

### Participants and Procedures

A community-based multiple screening program was designed and performed in Keelung, the northernmost county of Taiwan. The Keelung Community-based Integrated Screening (KCIS) was a mass screening program aimed at detecting 5 prevalent neoplasms (cervical, breast, hepatocellular, colorectal, and oral cancer) and 3 chronic diseases (hypertension, diabetes, and hyperlipidemia). The detailed study design and implementation have been given elsewhere (Chen *et al.*, 2004). The current study was a part of the KCIS program and was designed as a randomized controlled trial in 2000.

The 28,167 individuals aged 15 years or older who were invited to the KCIS program during 2000 are described in the Fig. We excluded 17,890 who lacked oral habits such as cigarette smoking or chewing betel quid. Of the



**Figure.** Trial profile of all eligible individuals.

remaining 10,277 eligible individuals, 2,302 refused to participate in the randomization study, and 7,975 participants were enrolled during January 1 to December 31, 2000, after signing a written informed consent. A structured questionnaire administered by public health nurses collected demographic information, as well as information on detailed oral habits such as cigarette smoking or betel quid chewing, in a face-to-face interview.

Enrolled participants were randomly allocated to either the experimental or the control group according to a random number table at each screening event. No other restriction on randomization was used. The experimental group was given toluidine blue solution for oral gargling, whereas the control group was given a placebo prepared with dye. An independent research assistant prepared all the toluidine blue and placebo dye with the same color judged by the naked eyes. No other solutions used, including acetic acid and distilled water, differed between the groups. Trained public health nurses instructed all participants to follow identical oral gargling procedures regardless of their allocated groups. Gargling procedures in the current study were similar to those previously published (Warnakulasuriya and Johnson, 1996), which adopted 10 mL of 1% toluidine blue as the staining solution for 1 min and 10 mL of 1% acetic acid as pre- and post-rinses for 20 sec.

Each participant was visually examined by one of six dentists who had had a dental practice for at least 3 yrs after graduation. They were trained by one senior oral pathologist from National Taiwan University Hospital, the largest medical center in Taiwan, with heuristic lectures before conducting this study. In the field work, they used disposable wooden tongue depressors under the illumination of a flashlight. The presence of any visible lesion in the oral cavity (*e.g.*, abnormal mucosal lesions related to OPMLs and other suspected lesions such as lichen planus, oral ulcer, hyperkeratosis, candidiasis, and so on) was recorded as screen-positive. The screen-positive participants were referred to the National Taiwan University Hospital for a

definite clinical diagnosis within 10 to 14 days, to reduce false-positivity (Mashberg, 1980, 1981). All the referred participants were then evaluated by the same oral pathologist, and biopsies were arranged if oral lesions were present. The formal pathological report was interpreted and issued by this oral pathologist only to avoid interobserver discrepancies. This report was used as the gold standard for final diagnosis.

Applying the placebo dye during the gargling procedure reduced the possibility of rendering the examiner aware of the participants' group allocations. The participants, the public health nurses, and all other personnel participating in the screening were unaware of the allocation of the groups, even after the completion of the screening. Allocation of the groups was not disclosed until the analysis of the results after the trial.

Diagnostic criteria (Kramer *et al.*, 1978), examination procedures, and documentation formats were discussed, taught, and calibrated in advance for all personnel participating in the study. We retrieved the occurrence of oral cancer, survival status, and causes of death of the studied participants by linking the entire cohort with the National Cancer Registry and the National Household Registry until December 31, 2004. The trial was approved by the local ethics committee of the Health Bureau in Keelung, including linkage to the health care registration data while maintaining participants' confidentiality.

## Statistical Analysis

According to the author's published survey on the prevalence of OPMLs (Yen *et al.*, 2007), a 20% increase in the detection rate of OPMLs with toluidine blue oral gargling as an adjunctive tool for visual screening required that each group have at least 3,954 participants for 80% statistical power and a 5% significance level.

Comparison between the study groups was performed with *t* tests or  $\chi^2$  tests as appropriate. The mean values were reported, followed by standard deviations. The annual incidence rate of oral cancer and the malignant transformation rate of OPMLs were estimated for each group, with a relative rate ratio and 95% confidence intervals. *P*-values < 0.05 were considered to be statistically significant.

## RESULTS

The profile of study enrollment, screening results, and occurrence of oral cancer for 7,975 participants is given in the Fig. Among them, 4,080 (51.2%) participants were randomly allocated to the experimental group and 3,895 (48.8%) to the control group (Fig.). The experimental group included 389 (9.5%) screen-positive individuals, and the control group included 322

**Table 1.** Baseline Characteristics and Referrals of Participants

	Experimental Group		Control Group		p-value
	Number of Cases	%	Number of Cases	%	
Sex					
Male	3719	91.2	3550	91.1	
Female	361	8.8	345	8.9	0.99
Mean age (yrs)	44.9 ± 14.4		44.6 ± 15.3		0.36
Age groups (yrs)					
< 30	611	15.0	688	17.7	
30–39	922	22.6	907	23.3	
40–49	1156	28.3	1009	25.9	
50–59	685	16.8	555	14.2	
60–69	442	10.8	416	10.7	
70–79	226	5.6	273	7.0	
>80	38	0.9	47	1.2	0.31
Screening results					
Positive	389	9.5	322	8.3	
Negative	3758	90.5	3573	91.7	0.047
Compliance with referral	320	7.8	293	7.5	0.59

**Table 2.** Distribution and Detection Rate of Screen-detected Oral Premalignant and Malignant Lesions

Results of Oral Lesions Detected after Referral	Experimental Group (n = 4080)		Control Group (n = 3895)		Rate Ratio	95% Confidence Intervals	p-value
	n	%	n	%			
Negative	55	1.3	59	1.5	0.82	(0.55–1.24)	0.13
Non-OPMLs	78	1.9	64	1.6	1.15	(0.79–1.68)	0.46
All OPMLs and malignant lesions	187	4.6	170	4.4	1.05	(0.74–1.41)	0.92
Oral submucous fibrosis	41	1.0	22	0.6	1.79	(1.06–3.01)	0.03
Homogeneous leukoplakia	125	3.1	131	3.4	0.79	(0.57–1.09)	0.16
Non-homogeneous leukoplakia	13	0.3	11	0.3	1.08	(0.48–2.46)	0.84
Erythroplakia	7	0.2	6	0.2	1.07	(0.36–3.22)	0.90
Oral cancer	1	0.02	0	0	n/a	n/a	n/a

OPMLs, oral premalignant lesions; n/a, not applicable.

(8.3%) (Fig.). Of these screen-positive participants, we ascertained 2 oral cancers out of the 320 (82.3%) who complied with the referral in the experimental group, and also 3 oral cancers out of the 293 (91.0%) who complied in the control group (Fig.), while there was no oral cancer among the non-compliant screen-positives in the two arms. There were 3 oral cancers ascertained by the end of the follow-up among the screen-negatives in each arm. One oral cancer occurred among the 2302 non-participants. Case numbers of the overall study and of each category of OPMLs are also presented in the Fig. No adverse events or effects happened during the screening.

There were no significant differences in sex, mean age, distribution of 10-year age groups, or compliance with referral between the groups (Table 1). Although the initial screen-positive rate was higher in the experimental group (9.5% vs. 8.3%,  $p = 0.047$ ) (Table 1), no significant differences were found in the detection rate of either OPMLs (4.6% vs. 4.4%) or non-OPMLs (1.9% vs. 1.6%) after referral (Table 2). However, 5% more OPMLs were

detected in the experimental group than in the control group, with a detection rate ratio of 1.05 (95% CI 0.74–1.41) (Table 2), but this difference was not significant. Among the various types of OPMLs detected, 79% more cases of OSF (41 vs. 22) were detected in the experimental group, with a detection rate ratio of 1.79 (95% CI 1.06–3.01) (Table 2). Differences in the detection rates of homogeneous leukoplakia, non-homogeneous leukoplakia, and erythroplakia were not statistically significant between groups (Table 2). Ancillary analysis of the detection rate of OPMLs at different buccal anatomical subsites, as defined by 2002 AJCC cancer staging (Greene *et al.*, 2002), revealed no statistical difference between groups ( $p = 0.30$ ).

Table 3 shows oral cancers detected at screening that resulted from malignant transformation of oral premalignant lesions, as well as follow-up of screen-negative participants. The malignant transformation rate among the screen-positive participants ( $129 \times 10^{-5}$ ) was lower than that ( $420 \times 10^{-5}$ ) in the control group (Table 3). The relative transformation rate ratio was 0.31 (95%

**Table 3.** Oral Cancers Identified by Different Scenarios between Both Groups

	Experimental Group	Control Group
1. Detected at first screening	1	0
2. Malignant transformation		
Oral submucous fibrosis → Oral cancer	0	1
Homogeneous leukoplakia → Oral cancer	1	1
Non-homogeneous leukoplakia → Oral cancer	0	0
Erythroplakia → Oral cancer	0	1
3. Screening negative → Oral cancer	3	3
4. Malignant transformation to cancer for OPML		
Cancer cases	1	3
Person-years	774.4	715.1
Malignant transformation rate ( $\times 10^{-5}$ )	129	420
5. Incidence of oral cancer		
Cancer cases	5	6
Person-years since randomization	17,944.7	16,940.8
Incidence rate of oral cancer ( $\times 10^{-5}$ )	28.0	35.4

CI 0.03–2.94), which was not statistically significant. The relative rate of incidence of oral cancer between the two groups ( $28.0 \times 10^{-5}$  vs.  $35.4 \times 10^{-5}$ ) was 0.79 (95% CI 0.24–1.23), indicating a lack of statistical significance (Table 3).

## DISCUSSION

Accumulating evidence has shown that oral cancer almost always develops at the location of pre-existing oral premalignant lesions, and that the malignant transformation occurs around 5 to 15 years later (Shiu *et al.*, 2000). Consequently, this long natural history provides an opportunity for the identification of OPMLs by proper screening before the occurrence of malignancy.

Based on previous findings that cigarette smoking and betel quid chewing are two significant independent risk factors for OSF and leukoplakia (Shiu *et al.*, 2000; Lee *et al.*, 2003), the current study was designed as a scientific randomized controlled trial to assess the effect of toluidine blue in facilitating the detection of more OPMLs, thereby reducing the incidence rate of oral cancer over long-term follow-up in individuals with either of these habits. After screening and waiting 10–14 days to minimize false-positives derived from factors such as inflammation or trauma to the oral mucosa, as suggested by Mashberg (1980, 1981, 1984), Lullmann-Rauch (1989), and Silverman *et al.* (1984), we found that the detection rate of OPMLs in the toluidine blue group was not significantly higher than that in the merely visual screening group. Furthermore, the 21% reduction in the incidence of oral cancer in the toluidine blue screening group after 5 years of follow-up was not significantly different from that in the visual screening group. This lack of statistical significance may be partly due to a non-significant difference in

detecting a larger proportion of OPMLs, and partly to insufficient statistical power after follow-up of only 5 years.

Because different examiners, such as trained volunteers (Mathew *et al.*, 1997), health workers, or primary care practitioners (Prout *et al.*, 1997), may influence the accuracy and yield of screening, only the most experienced dentists with the highest reported detection rate yield (Patton, 2003) performed visual screening in the current study. This might explain why a higher detection rate of OPMLs with toluidine blue compared with visual screening alone was not observed in the current study, since minute or concealed oral mucosal lesions were less likely to be missed by the experienced dentists in the current study. Improved training of dentists, rather than the use of toluidine blue, may also yield improved detection rates. Moreover, the light source used in the current study may not have provided enough illumination compared with those used in similar studies, which would prevent toluidine-blue-stained oral mucosal lesions from being detected. However, in the mass community-based screening setting, the flashlight is the most widely available, accessible, and convenient light source. These factors justify the use of the flashlight in our study.

With the aid of toluidine blue, significantly (79%) more OSF could be detected compared with visual screening alone in the current study. Since one of the histological changes of OSF is an abnormally high accumulation of collagen in the submucosal region, it is possible for toluidine blue to stain this acidophilic component with higher affinity (Mashberg, 1980). However, further histopathologic evaluations are required to bolster our finding. Moreover, since the malignant transformation rate of OSF was reported to be lower than that of other OPMLs (Lullmann-Rauch, 1989), whether a higher detection rate of OSF together with effective intervention may lead to a reduced incidence of oral cancer is of great interest. Nonetheless, OSF constitutes only a small fraction of OPMLs, and the numbers of detected OSF in the current study are still small. To validate this postulate requires a dedicated long-term follow-up and large-scale OSF cohort.

The annual transformation rate from leukoplakia to oral cancer in the screening-detectable phase was estimated to be  $6.05 \times 10^{-3}$  (95% CI 4.36–7.55  $\times 10^{-3}$ ) (Shiu and Chen, 2003). Shiu and Chen (2004) also reported the theoretical malignant transformation rate (MTR) to be  $9.79 \times 10^{-3}$ , and after intervention of OPMLs, the MTR decreased to  $2.67 \times 10^{-3}$ , which was close to the currently observed MTR of  $2.69 \times 10^{-3}$  in the screen-positive individuals ( $1.29 \times 10^{-3}$  in the experimental group and  $4.20 \times 10^{-3}$  in the control group). This suggested that the effects of interventions, such as excision of the OPMLs (Pandey *et al.*, 2001) or cessation of high-risk oral habits after referral of screen-positive participants, benefited both groups.

Two possible limitations to our study exist. First, the five-year follow-up duration may be relatively short with regard to the long natural history of OPML malignant transformation (Shiu *et al.*, 2000). However, because the major aim of our study was to assess whether toluidine blue as an adjunctive tool for visual screening can enhance the detection rate of OPMLs, given our limited budget, the sample size estimated in the current study cannot satisfy the goal of reducing incidence rates of oral cancer as the primary endpoint. Another five-year follow-up is mandatory to confirm this postulate by re-analysis of oral



cancer incidence from this cohort through linkage with the National Cancer Registry in future research. Second, although the 2302 non-participants included higher proportions of females and older individuals, they had a distribution of biological markers, including fasting blood sugar, total cholesterol, and triglycerides, similar to that of those enrolled in the screening program. Of the non-participants, we identified 1 oral cancer after 5 years of follow-up. The incidence rate ( $9 \times 10^{-5}$ ) among non-participants was lower than that of the control group ( $35.4 \times 10^{-5}$ ), since the percentage of females was higher in these non-participants than in the control group. This may limit the generalizability of our results to similar populations with high-risk oral habits, but it would not affect the internal validity of the results because of the randomized study design.

In conclusion, we demonstrated that using toluidine blue as an adjunctive tool for visual screening can detect significantly more oral submucous fibrosis and slightly more leukoplakia among high-risk individuals with habits of cigarette smoking or betel quid chewing as compared with visual screening alone. The five-year follow-up period might have been relatively short for a significant reduction in incidence rates of oral cancers to be observed, and the question merits further long-term follow-up.

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