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Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India

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SUMMARY

Objectives: We studied oral cancer incidence and mortality and the impact of compliance to repeat screening rounds during a 15-year follow-up in a cluster-randomized controlled trial in Trivandrum district, Kerala, India.

Methods: Healthy individuals aged 35 and above in seven clusters randomized to the intervention arm received four rounds of oral visual inspection by trained health workers at 3-year intervals, and those in six clusters randomized to the control arm received routine care during 1996–2005 and one round of visual screening during 2006–2009. Screen-positive persons were referred for diagnosis and treatment. Oral cancer incidence and mortality were compared between the study arms by intention to treat analysis.

Results: Of the 96,517 eligible subjects in the intervention arm, 25,144 (26.1%) had one, 22,382 (23.2%) had two, 22,008 (22.8%) had three and 19,288 (20.0%) had four rounds of screening. Of the 95,356 eligible subjects in the control group 43,992 (46.1%) received one round of screening. Although the 12% reduction in oral cancer mortality in all individuals did not reach statistical significance, there was a 24% reduction in oral cancer mortality (95% CI 3–40%) in users of tobacco and/or alcohol in the intervention arm after 4-rounds of screening; there was 38% reduction in oral cancer incidence (95% CI 8–59%) and 81% reduction in oral cancer mortality (95% CI 69–89%) in tobacco and/or alcohol users adhering to four screening rounds.

Conclusion: Sustained reduction in oral cancer mortality during the 15-year follow-up, with larger reductions in those adhering to repeated screening rounds support the introduction of population-based screening programs targeting users of smoking or chewing tobacco or alcohol or both in high-incidence countries.

Introduction

Oral cancer (International Classification of Diseases 10th edition codes C00-06) accounted for an estimated 264,000 new cases and 128,000 deaths globally in 2008; of these, 172,000 cases and 97,000 deaths occurred in less developed countries of the world.[1] India accounted for a fifth of the global burden at 45,500 cases and 31,100 deaths.[1] The high incidence in the Indian sub-continent[2] is related to the high prevalence of pan-tobacco chewing in the population, in addition to bidi and cigarette smoking as well as alcohol drinking.[3–5] Avoiding these risk factors can prevent a large proportion of oral cancers. Whereas 5-year survival exceeds 80% following diagnosis and treatment of early, localized (stages I and II) oral cancer, it drops to less than 20% with advanced clinical stages (III and IV).[6–9] Although the direct accessibility and visibility of the oral cavity for physical examination greatly facilitates early detection of preclinical invasive oral cancers and potentially malignant disorders (PMDs), a high proportion of oral cancer is still diagnosed in advanced clinical stages in most countries.[6–9] In 2005, we reported a 34% reduction in oral cancer mortality in high-risk individuals with tobacco chewing or smoking or alcohol drinking habits following three rounds of oral visual screening at 3-year intervals in a cluster-randomized controlled trial, after 9 years of

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follow-up since its initiation in 1996.[10] We now present the results after 15 years of follow-up in this trial and discuss the efficacy of adherence to repeated screening rounds.

Materials and methods

Participants and procedures

The methods of this cluster-randomized trial were described in detail elsewhere.[10–12] The study protocol was reviewed and approved by the scientific and ethics review committees of the Regional Cancer Centre, Trivandrum, India (RCC) and the International Agency for Research on Cancer, Lyon, France (IARC). In brief, the 13 panchayaths (municipal administrative units), in the Trivandrum District, Kerala, India chosen for the study were randomly assigned to two groups of seven and six clusters by blocked randomization; the two groups were then randomly assigned to receive oral visual screening by trained health workers (HWs) at 3-year intervals (seven clusters) or to a control group (six clusters) to receive existing care. The study was initiated in January 1996 and the results reported here are based on follow-up through December 2010.

Screening was provided by HWs, who were non-medical university graduates, trained to perform visual inspection of the oral mucosa and identify potential precancerous lesions (e.g., homogeneous leukoplakia, non-homogeneous leukoplakia, erythroplakia, oral submucous fibrosis) or oral cancer. Two manuals on visual inspection with color photographs and descriptions of oral lesions were used for training and reference during screening.[13,14]

Eligible participants were apparently healthy persons aged 35 years and older living in the study clusters with no past history of oral cancer. Two HWs were assigned to each cluster to visit households to identify and interview the eligible subjects during each round. The eligible subjects were explained about the study and a written informed consent was obtained. Information on house number, address, type of house, income, name, age, and personal habits of each resident in the household were collected and documented in a household form. Eligible individuals were then interviewed for details on occupation, habits, such as chewing, tobacco smoking, and alcohol drinking. The harmful aspects of tobacco or alcohol use were explained and subjects were advised to stop or not initiate these habits. The HWs screened the eligible persons in the intervention clusters during house visits. Screening was repeated every 3 years for four rounds, with all rounds completed in 2008. Oral mucosa was carefully inspected in bright daylight with the help of a torch light and palpated when necessary. The findings were recorded as normal; referable lesions suggestive of potentially malignant disorders, or suspicious ulcer, or growth suggestive of cancer. Screen-positivity was defined as the presence of referable lesions.

Eligible subjects in the control clusters were not screened but continued to receive routine health-care during the years 1996–2005. Once significant oral cancer mortality reduction following three rounds of screening among the high-risk subjects in the intervention arm was confirmed, the control subjects were offered screening during the years 2006–2008.

All screen-positive subjects were referred to a weekly clinic in the study project office where dentists and oncologists, with special training and several years of experience in the diagnosis of oral lesions, clinically examined them using standardized criteria[13,14] and advised on further steps. They assessed the oral cavity and documented the findings as normal, benign lesions, oral precancerous lesions or invasive cancer and advised the individuals to discontinue chewing, smoking and drinking and to improve oral hygiene. Punch or incision or excision biopsies were directed from oral precancerous lesions with a high degree of clinical suspicion of cancer and all growths; the biopsy specimens were processed at the RCC and histological findings were reported by one pathologist (ST). The reference investigation for final diagnosis of oral precancerous lesions was clinical examination by doctors and histology for all invasive oral cancers. Oral precancerous lesions were surgically excised whenever possible and biopsies were directed whenever progression was clinically suspected during follow-up.[15] Those with confirmed oral cancers were referred for appropriate treatment with surgery and/or radiotherapy and/or chemotherapy.

The study was monitored using a set of process measures such as participation in screening, screen positivity (the proportion of screened persons with a positive screening test), compliance to referral (the proportion of screen-positive subjects reporting for diagnostic confirmation in the weekly clinic) and intermediate outcome measures such as stage distribution of oral cancer cases, case fatality (proportion of deaths among oral cancer cases), and survival of oral cancer patients in the intervention and control arms.

The final outcome measures were oral cancer incidence and mortality in the study groups. We obtained information on the incident oral cancer cases in the study clusters from the Trivandrum population-based cancer registry, hospital cancer registry of the RCC and medical records departments of other hospitals treating oral cancer patients. This information was collected without being aware of study group assignment of cases. The staging of oral cancers was done according to the UICC TNM staging system.[16] Information on all deaths among the subjects was collected from the municipal and district death registers, hospital medical records, death records of churches and mosques, house visits by the population cancer registry staff and by project HWs. The cancer cases were coded by the ICD-O 3rd edition codes[17] and cause of death was coded using ICD-10[18] by the registry and project staff. We classified cases of oral cancer in the intervention arm as screen detected (diagnosed following a positive screen); interval (diagnosed after a negative screening test between screening rounds); and occurring among non-participants. The cause of death in each oral cancer case was assessed on a case-by-case basis by three physicians (KR, GT, ST) blinded to the study group allocation based on clinical information from medical records, death certificates and other details obtained during house visits and telephone enquiries. Deaths were attributed to oral cancer if the patient had histologically or clinically confirmed oral cancer, lymph nodes or distant metastasis at the time of death or had died due to complications of oral cancer treatment. The registered oral cancer cases and deaths were then classified, as belonging to the intervention or control arm or to subjects not in the study, by matching with the study database on case-by-case basis by the screening project staff.

Statistical analysis

Data were entered in D-Base and analyzed using STATA 9.2 software package. Analysis was by intention-to-treat principle: taking into account the cluster randomization. Participation in screening, screen positivity, compliance for referral, stage distribution, and case fatality were calculated as proportions and survival was computed by Kaplan–Meier analysis.[19] The comparison of proportions between the study groups was performed using a Mann–Whitney non-parametric test based on all cluster summary data.[20]

For calculation of oral cancer incidence rates, the numbers of person years in the study groups were estimated from the date of the study initiation (January 1, 1996) to December 31, 2010 or the date of diagnosis, death or migration, whichever occurred first. For calculation of oral cancer mortality rates, the person-years were estimated from the date of study initiation to December 31, 2010 or the date of death or migration, whichever occurred first. Multivariate analysis of oral cancer incidence and mortality hazard

ratios with 95% confidence intervals (CIs) was done using Cox proportional hazards regression, taking into account the cluster design and adjusting for age, sex, and total number of residents.[21] The effect of compliance with screening was evaluated by the risk of oral cancer incidence and mortality in individuals who participated in a specific number of repeated screening rounds relative to the risk in the control group. The study was planned to have an 80% power at 5% significance level to detect a 35% reduction in cumulative mortality rate from oral cancer within 12 years of enrolment between the intervention and control groups; sample size considerations have been detailed elsewhere.[10,11]

Results

Fig. 1 shows the study profile in terms of eligible subjects, person-years, oral cancer incidence and mortality rates in all individuals; Fig. 2 shows the above in users of tobacco or alcohol or both. The study groups had similar distribution of age, sex, religion, house type, education, occupation, income, pan tobacco chewing, tobacco smoking, and alcohol drinking as detailed elsewhere.[10] The total number of eligible individuals, screened individuals, screen-positive individuals, and screen-positives who complied with referral to the study clinicians are given in Table 1. The proportion of eligible individuals screened in each round varied between 82.1% in the first round and 44.5% in the fourth round; the screen-positivity rate was 7.3% (3589/49,179) in the first, 2.6% (1475/55,993) in the second, 2.1% (1395/64,898) in the third and 2.2% (932/43,014) in the fourth rounds.

Overall, of the 5586 ever screen-positive individuals, 3298 (59.0%) complied with referral to the study clinicians; of these, 770 (23.3%) had healthy mucosa or benign lesions; 2336 (70.8%) were diagnosed with oral precancerous lesions (lichen planus $N = 53$; homogeneous leukoplakia $N = 898$; non-homogeneous leukoplakia $N = 812$; submucous fibrosis $N = 573$); and 192 (5.8%) with growths suspicious of cancer. Of the 2336 individuals with

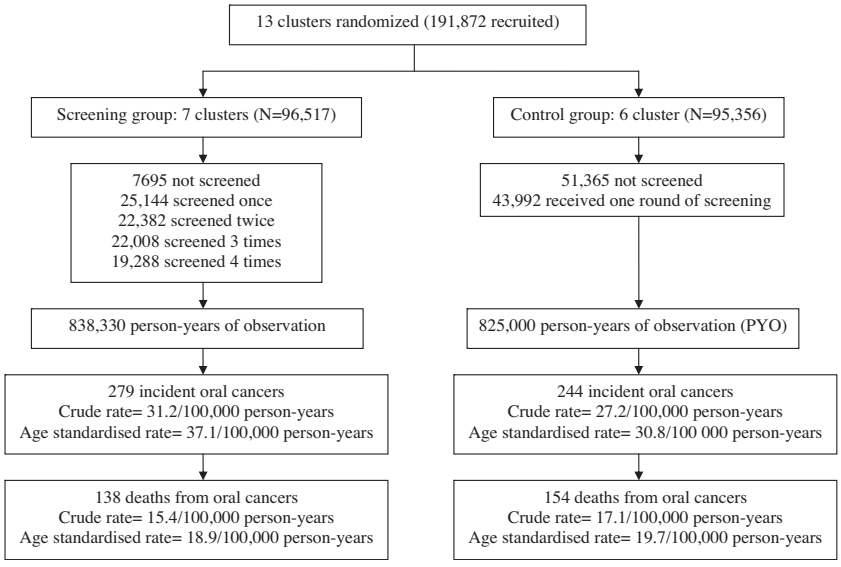

Figure 1 Trial profile of all eligible individuals.

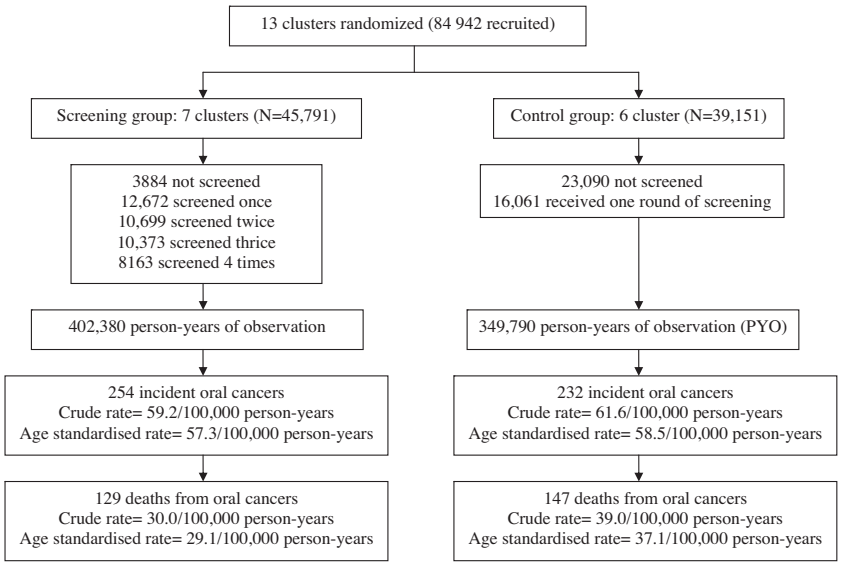

Figure 2 Trial profile of individuals with tobacco or alcohol drinking or both habits.

Table 1
Screening process by round of screening.

Variable	Intervention group (seven clusters, 96,517 individuals)					Control group (six clusters, 95,356 individuals)
	1st Round (1996–1998)	2nd Round (1999–2001)	3rd Round (2002–2004)	4th Round (2006–2009)	Overall (1996–2009)	4th Round (2006–2009)
Total eligible individuals	62,288	67,621	73,028	96,517	96,517	95,356
Screened individuals	49,179	55,993	64,898	43,014	88,822	43,992
Screen-positives	3589	1475	1395	932	5586	1163
Screen-positives who complied with clinical assessment by doctors in the project clinic	1886	816	883	185	3298	189

Table 2
Distribution of stage by number of times screened.

Number of times screened	Clinical stage										Total
	I		II		III		IV		Unknown		
Screening group											
0	0	(0%)	3	(16%)	3	(16%)	7	(37%)	6	(32%)	19
1	9	(11%)	10	(13%)	18	(23%)	32	(41%)	10	(13%)	79
2	10	(15%)	11	(17%)	17	(26%)	25	(38%)	3	(5%)	66
3	23	(32%)	12	(17%)	9	(13%)	25	(35%)	3	(4%)	72
4	17	(40%)	15	(35%)	4	(9%)	7	(16%)	0	(0%)	43
Total	59	(21%)	51	(18%)	51	(18%)	96	(34%)	22	(8%)	279
Control group											
1996–2004	21	(13%)	19	(12%)	34	(22%)	72	(46%)	12	(8%)	158
0	0	(0%)	7	(16%)	12	(27%)	20	(44%)	6	(13%)	45
1	10	(24%)	9	(22%)	6	(15%)	15	(37%)	1	(2%)	41
Total	31	(13%)	35	(14%)	52	(21%)	107	(44%)	19	(8%)	244

oral precancerous lesions 499 (21.4%) with suspicious features of occult cancer had directed biopsies and 26 were histologically diagnosed as normal, 133 as hyperkeratosis, 121 as mild dysplasia, 172 as moderate dysplasia, 25 as severe dysplasia and 22 as squamous cell carcinoma. Of the 192 with suspicious growth, biopsy revealed 163 as squamous cell carcinoma, 3 as verrucous carcinoma, 4 as severe dysplasia, 7 as moderate dysplasia, 3 as mild dysplasia, and 12 as hyperkeratosis. The detection rate of oral precancerous lesions and oral cancer in the first, second, third and fourth rounds were 28.3, 11.9, 11.6 and 3.9 per 1000 screened individuals, respectively. Of the 95,356 individuals in the control arm, 43,992 (46.1%) had one round of screening during 2006–2008 and 1163 (2.6%) were positive.

Of oral cancer cases, 279 (188 screen-detected, 72 interval cancers and 19 in those who did not respond to any screening round) were diagnosed in the intervention arm and 244 in the control group during 1996–2010 (Table 2). The intra oral site distribution in the intervention arm was: lip 7 (2.5%); tongue 83 (29.8%); gingiva 19 (6.8%); floor of mouth 7 (2.5%); hard palate 18 (6.5%); and buccal mucosa 145 (52.0%). The site distribution in the control group was: lip 7 (2.9%); tongue 89 (36.5%); gingiva 29 (11.9%); floor of mouth 13 (5.3%); hard palate 12 (4.9%); and buccal mucosa 94 (38.5%). All invasive cancers were confirmed histologically: in the intervention arm 273 (97.9%) were squamous cell carcinoma, 4 (1.4%) were verrucous carcinoma, 1 mucoepidermod and 1 spindle cell carcinoma; in the control group 242 (99.2%) were squamous cell carcinoma, 1 was verrucous carcinoma, and 1 was mucoepidermoid carcinoma.

The stage distribution of oral cancer cases in the study arms is given in Table 2; 39.4% of the cases in the intervention arm were in stages I or II compared with 27.0% cases in the control arm ($p = 0.002$). A significantly higher 5-year survival (55.5% vs. 43.4%) and 10-year survival (48.3% vs. 30.6%) was observed in the intervention arm than in the control arm ($p = 0.003$). Table 3 shows the number of oral cancer cases, stage III or worse cases, oral cancer deaths, incidence and mortality rates and hazard ratios with 95% CI in all eligible persons, as well as in those with and without tobacco and/or alcohol habits in the intervention and control arms. There were 138 and 154 oral cancer deaths in the intervention and control arms, respectively. No significant reduction in cumulative oral cancer incidence and there was a statistically non-significant 12% reduction in oral cancer mortality in all individuals in the intervention arm compared with the control arm. There was a significant 21% reduction in the incidence of advanced oral cancers and a significant 24% reduction in oral cancer mortality in users of tobacco or alcohol or both in the intervention arm compared with the controls (Table 3). The cumulative incidence of all oral cancers, of stage II or worse cancers, of stage III or worse cancers and of cumulative mortality from oral cancer in tobacco and/or alcohol users are shown in Fig. 3.

The effect of compliance with the repeated screening rounds in terms oral cancer incidence and mortality hazard ratios and their 95% confidence intervals (CIs) compared with controls is given in Tables 4 and 5. There was a significant 38% reduction and 79% reduction in oral cancer mortality in all eligible individuals adhering to three and four screening rounds, respectively (Table 4). Table 5 shows the effect of compliance with repeated screening rounds in those with tobacco or alcohol or both habits. There was a statistically significant 38% reduction in incidence in those who had four screens and 47% reduction and 81% reduction in oral cancer mortality in those who complied with three and four screening rounds, respectively.

There were neither instances of severe adverse events, such as death, vaso-vagal attack, anaphylactic reaction, major bleeding, hospitalization, infection, severe pain, or other adverse effects, nor major cosmetic or functional disabilities as a consequence of screening, directing biopsies, or excision of lesions. There was one case of mild bleeding following biopsy, which required suture.

Table 3
Oral cancer incidence, stage III or worse incidence and mortality rates in all eligible individuals, in eligible individuals with tobacco or alcohol drinking habits or both and in eligible individuals with no habits.

	Screening group	Control group	Rate ratio (95% CI)[a]
Overall			
Person-years of observation	895,310	898,280	
Number of oral cancer cases	279	244	
Incidence rate (per 100,000)	31.2	27.2	1.14 (0.91–1.44)
Number of stage III or worse oral cancer cases	147	159	
Incidence rate (per 100,000)	16.4	17.7	0.92 (0.72–1.17)
Number of oral cancer deaths	138	154	
Oral cancer mortality rate (per 100,000)	15.4	17.1	0.88 (0.69–1.12)
Tobacco or alcohol users or both			
Person-years of observation	429,620	377,350	
Number of oral cancer cases	254	232	
Incidence rate (per 100,000)	59.2	61.6	0.97 (0.79–1.19)
Number of stage III or worse oral cancer cases	138	154	
Incidence rate (per 100,000)	32.2	40.9	0.79 (0.65–0.95)
Number of oral cancer deaths	129	147	
Oral cancer mortality rate (per 100,000)	30.0	39.0	0.76 (0.60–0.97)
People with no habits			
Person-years of observation	465,700	520,940	
Number of oral cancer cases	25	12	
Incidence rate (per 100,000)	5.4	2.3	2.34 (1.07–5.12)
Number of stage III or worse oral cancer cases	9	5	
Incidence rate (per 100,000)	1.9	1.0	2.01 (0.66–6.13)
Number of oral cancer deaths	9	7	
Oral cancer mortality rate (per 100,000)	1.9	1.3	1.36 (0.57–3.26)

[a] The reference category is the control group.

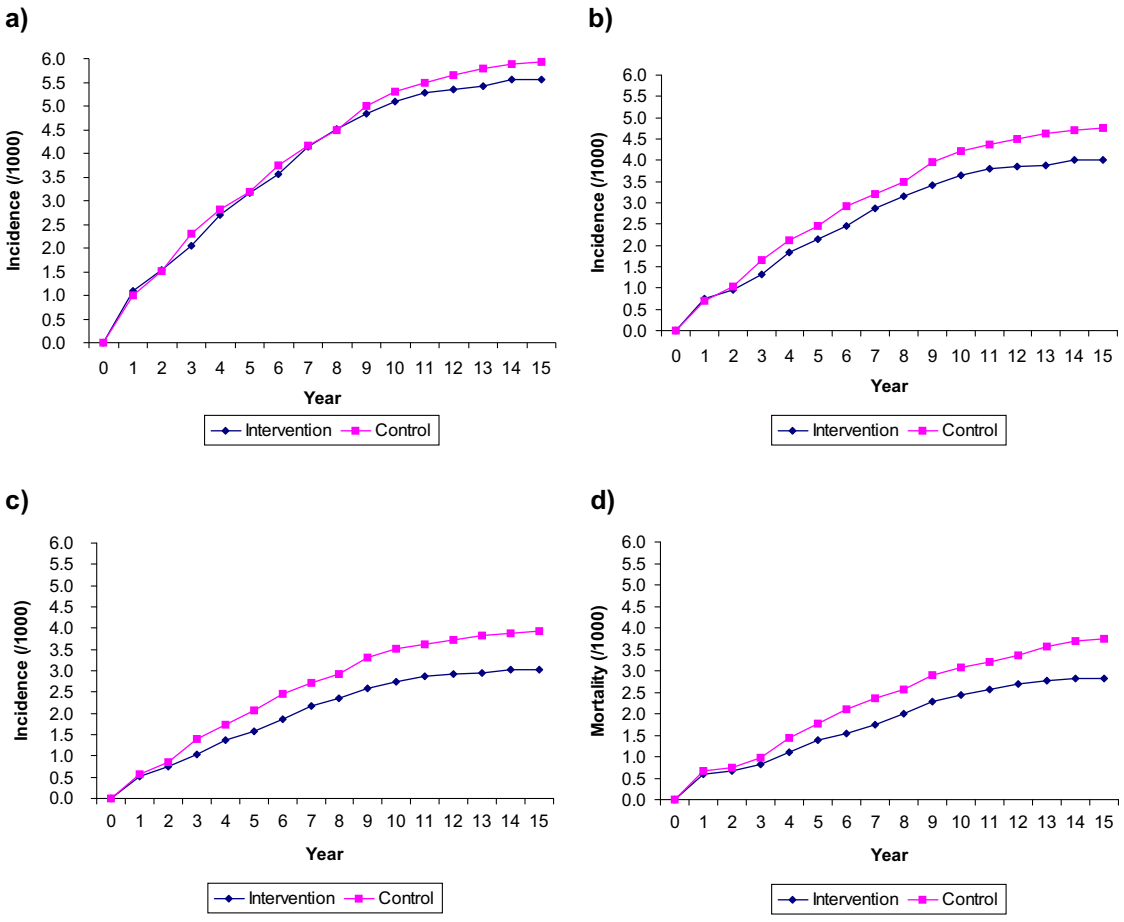

Figure 3 Cumulative incidence of (a) overall, (b) stage 2 or worse, (c) stage 3 or worse, and (d) mortality from oral cancer among individuals with tobacco or alcohol drinking or both habits.

Table 4
Oral cancer incidence/mortality rates by number of times screened among all participants.

Number of times screened	Cases/deaths	Person-years of observation	Incidence/ mortality rate per 100,000 PYO	Incidence/mortality hazard ratio[a] (95% CI)
Oral cancer incidence				
Control	244	897,610	27.2	1.00
Intervention				
0	19	34,910	54.4	1.43 (0.89–2.30)
1	79	129,230	61.1	1.94 (1.34–2.80)
2	66	204,130	32.3	1.14 (0.86–1.52)
3	72	259,870	27.7	1.08 (0.81–1.44)
4	43	266,240	16.2	0.76 (0.49–1.17)
Oral cancer mortality				
Control	154	898,280	17.1	1.00
Intervention				
0	13	34,900	37.2	1.46 (0.78–2.73)
1	57	129,290	44.1	2.26 (1.66–3.09)
2	33	204,330	16.2	0.94 (0.68–1.30)
3	27	260,220	10.4	0.62 (0.37–1.04)
4	8	266,560	3.0	0.21 (0.13–0.35)

PYO: person-years of observation.
[a] Adjusted for age, sex and total number of residents; CI: confidence interval.

Table 5
Oral cancer incidence/mortality rates by number of times screened among individuals with tobacco or alcohol drinking habits or both.

Number of times screened	Cases/deaths	Person-years of observation	Incidence/mortality rate per 100,000 PYO	Incidence/mortality hazard ratio[a] (95% CI)
Oral cancer incidence				
Control	232	376,690	61.6	1.00
Intervention				
0	13	18,530	70.2	1.01 (0.58–1.76)
1	72	69,520	103.6	1.62 (1.17–2.23)
2	61	102,870	59.3	0.97 (0.74–1.26)
3	68	125,770	54.1	0.90 (0.67–1.20)
4	40	112,020	35.7	0.62 (0.41–0.92)
Oral cancer mortality				
Control	147	377,350	39.0	1.00
Intervention				
0	11	18,520	59.4	1.27 (0.68–2.37)
1	52	69,580	74.7	1.90 (1.45–2.49)
2	32	103,070	31.0	0.83 (0.62–1.12)
3	26	126,110	20.6	0.53 (0.34–0.84)
4	8	112,330	7.1	0.19 (0.11–0.31)

PYO: person-years of observation; CI: confidence interval.
[a] Adjusted for age, sex and total number of residents.

Eight patients reported moderate pain 1 week after biopsy, which was controlled by anti-inflammatory drugs.

Discussion

We have demonstrated a sustained reduction in oral cancer mortality following oral visual screening in high-risk individuals who chewed betel quid with tobacco or smoked or drank alcohol in various forms in the intervention arm after 15 years from the beginning of the study, although the reduction in cumulative mortality was lower than the 34% reduction reported following three rounds of screening after 9 years from the initiation of the study.[10] The frequency of oral cancer cases and deaths among 106,929 individuals with no habits were 37 and 16, respectively as opposed to 486 and 292, respectively among the 84,943 individuals who used tobacco and/or alcohol indicating the low-risk of oral cancer in individuals not exposed to tobacco and/or alcohol habits. Since the low-risk individuals with no habits constituted 55.7% (N = 106,946) of the eligible subjects, our study lacked the power to detect significant oral cancer mortality differences in the general population. Our further discussion, therefore, mainly concerns the high-risk individuals with tobacco and/or alcohol habits. The reduction in oral cancer mortality was due to early detection by screening as shown by the significantly reduced incidence of advanced oral cancers, the increased survival and reduced case fatality in the intervention arm. The mortality reduction has been observed despite the modest adherence of screen-positive individuals for further assessment: among the 45,792 high-risk individuals in the intervention arm, 41,908 were screened at least once, 5246 (12.5%) were screen-positive and 3108 of those (59.3%) were seen by the study doctors for further diagnosis.

A cost-effectiveness study in the context of our trial established that oral visual screening was performed for under US$6 per person and the incremental cost per life-year saved was US$835 for all eligible individuals and US$156 for tobacco and/or alcohol users.[22] These are well below the per capita gross domestic product of India, indicating that the most cost-effective approach to oral cancer screening is to offer it to users of tobacco or alcohol or both.[22] There was no impact of screening on oral cancer incidence except in the high-risk group who had four rounds of screening. The wide exposure of oral epithelium to carcinogenic effects from tobacco and alcohol, leading to the field cancerization effect and

the modest compliance for repeated screening minimized the potential benefits of habit intervention, risk assessment, and follow-up of those with oral precancerous lesions might have on the incidence of new cancers. It is not clear if medical or surgical treatment of oral precancerous lesions is effective in preventing malignant transformation.[23,24] The benefits of adherence to repeated screening is well demonstrated by the impressive reduction of oral cancer mortality observed in both the high-risk individuals (Table 5) and all eligible individuals (Table 4) who had three or four screening rounds; there was an 79% or more oral cancer mortality reduction in those who had four rounds of screening. This enhanced mortality reduction is essentially due to the substantially improved early detection of oral cancer cases. In addition, there was a significant 38% reduction in oral cancer incidence in those high-risk individuals who had four screening rounds.

A Cochrane Review in 2010[25] based on our published results in 2005[10] concluded that a visual examination, as part of population-based screening, reduced oral cancer mortality rate in high-risk individuals, producing stage shift and improvement in survival across the population as a whole. In 2006, we commented that important issues to consider when implementing screening programs are not necessarily the same as those needed for scientific assessment of the effectiveness of a procedure and whether a technique should be part of a cancer prevention strategy depends on health priorities and health service resources in a given setting after issues such as the technique's effectiveness and public health importance of the disease have been assessed.[26]

The value of routine biopsy and histological assessment of oral precancerous lesions in predicting the risk of invasive cancer is not clear.[27–29] Reporting histological characteristics of oral precancerous lesions, including a histological diagnosis of dysplasia in oral lesions, is subjective and some studies reported no association of dysplasia or its grades with malignant transformation[27–29] while others found a positive association.[30,31] The frequency of malignant transformation of oral dysplasia over a 15-year follow-up in our study was 3.9% (13/322); these values were 6.8% (2/29) for severe dysplasia; 4.5% (8/179) for moderate dysplasia; 2.4% (3/124) for mild dysplasia and 4.5% (7/155) for lesions with hyperkeratosis indicating the poor predictive value of dysplasia for the likelihood of progression to cancer.

An expert panel of the American Dental Association (ADA)[32] concluded, based on level Ib evidence (evidence from at least one randomized trial), that community-based screening by visual and tactile examination may decrease oral cancer-specific mortality among people who use tobacco and/or alcohol. They recommended that clinicians should look for signs of precancerous lesions or early cancers while performing routine visual and tactile screening in all subjects, but particularly in those who use tobacco and/or alcohol and the life saving benefits for subjects with treatable lesions was more important than the potential harms incurred by those with benign or non-progressive lesions.[32]

The limitations of our study include the small number of clusters, the lack of documentation of quality of life, the modest compliance of screen-positive individuals for further assessment and the inclusion of elderly (70 years and above) individuals as eligible individuals. A small number of clusters were randomized due to the high population density in the study area and to reduce the risk of contamination between the study groups. Although interpretation of visual inspection may suffer from a degree of subjectivity, variations in testing between providers may be minimized by repeated training and careful monitoring of providers.[33] The strengths of our study include repeated training of the health workers to reduce false positive and false negative test outcomes, almost perfect agreement (kappa = 0.85) between the findings of the health workers and the physicians in identifying the different types of oral precancerous lesions,[33] the avoidance of over-treatment of screen-positives by conservative management of individuals with oral precancerous lesions and the provision of cancer treatment after histological confirmation of cancer avoided over-treatment of benign lesions; the low frequency of false-positive tests and the reliable long-term follow-up study participants by active and passive follow-up methods.

In summary, our findings support the routine use of oral visual screening to reduce oral cancer mortality among the high-risk of group of users of tobacco or alcohol or both in the general population, in addition to primary prevention efforts to reduce and prevent tobacco and alcohol use. We recommend that dentists and general practitioners perform a careful oral visual examination in tobacco or alcohol users during routine clinical interactions and refer those with suspicious oral lesions for early diagnosis and treatment. A public awareness program that stresses the importance of oral visual screening, once in 3 years, beginning at 35 years of age, warning signs of oral cancer and the hazards of tobacco and alcohol use and efforts to improve the clinical skills of primary care practitioners and dentists in the early detection and prompt referral of subjects with potentially malignant disorders as well as improving health care infrastructure for early diagnosis and adequate treatment of lesions can significantly contribute to reducing oral cancer mortality in high-risk countries.

Conflict of interest

None declared.

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