Oral cancer screening: 5 minutes to save a life

In today's *Lancet*, Rengaswamy Sankaranarayanan and colleagues report the first solid evidence that periodic examination of the oral cavity can reduce mortality from oral cancer in high-risk individuals. These results come from the Kerala screening trial, a cluster randomised trial, designed to have 80% power to detect a 35% reduction in oral cancer mortality within 12 years of enrolment between the intervention and control group, through rounds of screening every 3 years. The investigators report that, 9 years after the start of screening, there was a significant 32% reduction in mortality in high-risk individuals in the intervention group (42% when only male tobacco/alcohol users are considered). Overall, these data suggest that oral visual screening in high-risk patients could prevent about 40 000 deaths from oral cancer worldwide.

The reported data could be read in two ways. The first is the methodological evaluation of oral cancer screening itself. From this point of view, are the outcomes reported by Sankaranarayanan and colleagues adequately supported by the study design or do limitations exist? For example, the restricted-block randomisation can be potentially imbalanced when the number of clusters is small. Also, the recruitment of non-medical health workers raises concerns about the sensitivity and specificity to detect lesions and patients' compliance with referral. A screening interval of 3 years is long and the percentage of patients who did not get biopsy was high. Finally, clinical and histopathological diagnostic criteria were not clearly reported and variations in definitions and management of oral lesions can influence screening outcomes. On the other hand, the data suggest perhaps the right perspective in the fight against oral cancer—supporting prevention through screening as a potential major target of every health organisation worldwide. Oral cancer is a significant public-health threat, accounting for 270 000 new cases annually[1] and with one of the lowest survival rates (fewer than 50% of patients surviving more than 5 years). Furthermore, in the past few decades despite advances in the detection and treatment of many other malignancies, this rate has remained disappointingly low and relatively constant.

Rather than prevalence, the most peculiar characteristic of oral cancer is the apparently unexplainable imbalance between its global burden and the potential theoretical ease in decreasing morbidity and mortality with early detection. Oral cancer is almost always preceded by visible changes in the oral mucosa (figure, A and B), which allows clinicians to detect and treat effectively early intraepithelial stages of oral carcinogenesis.[2] Nevertheless, most oral cancers are currently detected at a late stage, when treatment is complex, costly, and has poor outcomes (figure, C and D). Paradoxically, the percentage of oral cancers diagnosed in the early stages is similar to that of colon cancers (36%).[3] Lack of awareness in the public of the signs, symptoms, and risk factors for oral cancer,[4] as well as a disappointing absence of prevention and early detection by health-care providers,[5] are both believed to be responsible for the diagnostic delay. It is strange to think that, at present, pelvic examination and Pap smears appear more acceptable than looking in the mouth,[6] for both patients and physicians. Current research mainly focuses on therapies for advanced oral cancers. As a result we have been spending hundreds of millions of dollars in treating patients, two-thirds of whom will die within 3–5 years, consuming educational

Figure: Oral precancer and cancer
5-min clinical examination of oral mucosa with only lighting, gauze, and gloves can easily detect potentially malignant lesions (A=leukoplakia of floor of mouth; B=leukoplakia of tongue). Identification should allow clinicians to detect early intraepithelial stages of oral carcinogenesis, such as mild, moderate, and severe dysplasia, and carcinoma in situ, which generally precede development of invasive oral squamous-cell cancer and, if appropriately managed, are often characterised by good prognosis. Nevertheless, most oral cancers are currently diagnosed at late stage (C=advanced cancer of tongue; D=advanced cancer of buccal mucosa), when local and lymphatic spread are already present, leading to a dramatically worse prognosis and increased treatment costs.

and scientific resources on procedures burdened by high costs and poor results, or on expensive molecular studies that are not easy to reproduce or can be applied to a small percentage of patients only.[7] It is now time for a new deal.

A first step has already been taken by WHO, which has recently issued a commitment to action against the neglected burden of oral cancer, mainly by strengthening prevention.[8] Nevertheless, so far, there has been no evidence to support the use of visual examination as a method of screening for oral cancer.[9] Sankaranarayanan and colleagues' data should lead health organisations to change, at least in part, their policy, transferring resources from conventional fields to new methods of preventive intervention with greater effectiveness and lower cost. We have to remember that screening for oral cancer is a simple non-invasive procedure, which needs only a 5-min visual inspection of the oral mucosa with lighting, gauze, and gloves, whereas the detection of most solid malignancies in their early asymptomatic stages almost always requires special, costly, and often invasive techniques. Visual screening for oral cancer is easy, effective, cheap, and saves lives.

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1   Ferlay J, Parkin DM, Pisani P. GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. Version 1.0, IARC Cancer Base No. 5. Lyon: IARC Press, 2004. http://www-dep.iarc.fr/ (accessed May 26, 2005).

2   Mignogna MD, Fedele S, Lo Russo L, Ruoppo E, Lo Muzio L. Costs and effectiveness in the care of patients with oral and pharyngeal cancer: analysis of a paradox. *Eur J Cancer Prev* 2002; **11:** 205–08.

3   Mashberg A. Diagnosis of early oral and oropharyngeal squamous carcinoma: obstacles and their amelioration. *Oral Oncol* 2000; **36:** 253–55.

4   Warnakulasuriya KA, Harris CK, Scarrott DM, et al. An alarming lack of public awareness towards oral cancer. *Br Dent J* 1999; **187:** 319–22.

5   Mignogna MD, Fedele S, Lo Russo L, Ruoppo E, Lo Muzio L. Oral and pharyngeal cancer: lack of prevention and early detection by health care providers. *Eur J Cancer Prev* 2001; **10:** 381–83.

6   Smart CR. Screening for cancer of the aerodigestive tract. *Cancer* 1993; **72:** 1061–65.

7   Mignogna MD, Fedele S, Ruoppo E, Lo Russo L. The role of molecular techniques in preventing oral cancer and improving its poor prognosis: an illusion? *J Oral Pathol Med* 2002; **31:** 246–48.

8   WHO. The Crete declaration on oral cancer prevention 2005—a commitment to action. April 19–24, 2005. http://www.who.int/oral_health/ events/crete_declaration_05/en/ (accessed May 26, 2005).

9   Kujan O, Glenny AM, Duxbury AJ, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database System Rev* 2003; Issue 4: CD004150, DOI: 10.1002/14651858.CD004150.

Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial

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Summary

Background Oral cancer is common in men from developing countries, and is increased by tobacco and alcohol use. We aimed to assess the effect of visual screening on oral cancer mortality in a cluster-randomised controlled trial in India.

Methods Of the 13 clusters chosen for the study, seven were randomised to three rounds of oral visual inspection by trained health workers at 3-year intervals and six to a control group during 1996–2004, in Trivandrum district, Kerala, India. Healthy participants aged 35 years and older were eligible for the study. Screen-positive people were referred for clinical examination by doctors, biopsy, and treatment. Outcome measures were survival, case fatality, and oral cancer mortality. Oral cancer mortality in the study groups was analysed and compared by use of cluster analysis. Analysis was by intention to treat.

Findings Of the 96 517 eligible participants in the intervention group, 87 655 (91%) were screened at least once, 53 312 (55%) twice, and 29 102 (30%) three times. Of the 5145 individuals who screened positive, 3218 (63%) complied with referral. 95 356 eligible participants in the control group received standard care. 205 oral cancer cases and 77 oral cancer deaths were recorded in the intervention group compared with 158 cases and 87 deaths in the control group (mortality rate ratio 0·79 [95% CI 0·51–1·22]). 70 oral cancer deaths took place in users of tobacco or alcohol, or both, in the intervention group, compared with 85 in controls (0·66 [0·45–0·95]). The mortality rate ratio was 0·57 (0·35–0·93) in male tobacco or alcohol users and 0·78 (0·43–1·42) in female users.

Interpretation: Oral visual screening can reduce mortality in high-risk individuals and has the potential of preventing at least 37 000 oral cancer deaths worldwide.

Introduction

Oral cancer is common in men in developing countries.[1] There were 274 300 new cases and 145 500 deaths worldwide in 2002, of which two-thirds took place in developing countries.[1] Although the disease is largely preventable by individuals avoiding risk factors such as tobacco or alcohol use, a high rate of oral cancer has been recorded in the Indian subcontinent, central and eastern Europe, parts of France, southern Europe, South America, and Oceania.[2] Oral cancer is the most common form of cancer and of cancer-related death in men in India.[1,2] Its high risk in the Indian subcontinent is related to the popularity of pan-tobacco (a combination of betel leaf, lime, arecanut, and sun-cured tobacco) chewing in the region.[3] A rising trend in oral cancer mortality has been recorded, especially in central and eastern Europe.[4]

Screening for oral cancer might be useful, because of the easily detectable precancerous lesions, early invasive cancers, and improved survival after treatment of early stage cancers. Visual inspection of the oral cavity is a simple, acceptable, and accurate screening test for oral neoplasia.[5–10] But will a visual, inspection-based screening programme lead to a substantial reduction in oral cancer mortality? We undertook a trial in 1996 to assess the efficacy of visual screening to reduce oral cancer mortality in a high-risk population in Kerala, India. This collaborative project was undertaken by the International Agency for Research on Cancer (IARC) of WHO and the Regional Cancer Centre (RCC).

Methods

Participants and procedures

Methods of this cluster-randomised trial have been described elsewhere.[11,12] Of the 13 clusters (panchayaths or municipal administrative units) in the Trivandrum district (Kerala, India) chosen for the study, seven were randomised to receive three rounds of oral visual screening by trained health workers at 3-year intervals, and six to a control group to receive standard care. The study protocol was reviewed and approved by the scientific and ethics review committees of the RCC and the IARC, Lyon, France.

Health workers were non-medical university graduates who received training at the beginning of the study to count the households in study clusters and the household members; to explain the study to eligible participants; to obtain informed consent; to obtain information on sociodemographic factors and personal habits by interviewing eligible participants, and to give messages aimed at preventing and reducing tobacco and alcohol use. The health workers assigned to the intervention clusters were trained to undertake oral

visual inspection, identify lesions suggestive of being precancerous in the oral cavity (eg, homogeneous leucoplakia, non-homogeneous leucoplakia, erythroplakia, oral submucous fibrosis), and identify oral cancer. Two manuals on visual inspection with colour photographs and descriptions of oral lesions were used for training and reference during screening.[13,14]

Eligible participants were apparently healthy people aged 35 years and older with no past history of oral cancer, who lived in the study clusters. Two health workers were assigned to every cluster to visit households to identify and interview the eligible individuals during every round of the study. Eligible participants were told about the study and written informed consent was obtained. Information on house number, address, type of house, income, name, age, and personal habits were obtained by use of a household form. Eligible individuals were then interviewed for details on occupation and habits, such as pan-tobacco chewing, tobacco smoking, and alcohol use. The harmful aspects of tobacco or alcohol use

were explained and those participants with habits were advised to stop and others were encouraged not to start these habits. Although control participants identified during house visits to control clusters were not screened, they continued to receive routine awareness messages and to use health-care facilities as usual.

Trained health workers screened eligible individuals in the intervention groups during house visits. Screening was repeated every 3 years for a maximum of three rounds, and was stopped in October, 2004. Oral visual inspection was undertaken in bright daylight and with the additional use of a flashlight. Labial and buccal mucosa, retromolar area, gingiva, anterior tongue, floor of mouth, and hard palate were carefully inspected and palpated when necessary. The findings were recorded as: normal or non-referable lesions (eg, fissures in the tongue, aphthous ulcers, black patches, blanching), referable lesions that were suggestive of precancerous lesions (eg, white lesions, ulcerated or nodular white lesions, verrucous lesions, red lesions, oral submucous fibrosis), or lesions suggestive of cancer (eg, suspicious ulcers or growths). Screen positivity was defined as the presence of one or more of the referable lesions. Screen-positive individuals were referred to reference investigations, and screen-negative individuals were advised to receive repeat screening after 3 years.

The screen-positive participants were referred to dentists and oncologists in specialised clinics who undertook clinical examination of the oral cavity and documented the findings as normal, benign lesions, oral precancerous lesions (lichen planus, homogeneous leucoplakia, non-homogeneous leucoplakia, oral submucous fibrosis), or invasive cancer. Biopsy samples were obtained from individuals with oral precancerous lesions and cancers that were clinically confirmed. One pathologist (ST) did histological reporting of all biopsy samples. The reference investigation for final diagnosis was clinical examination by doctors or histology (or both). Individuals with positive screens but showing no neoplasia were advised repeat screening after 3 years. Participants with oral leucoplakia were reviewed for surgical excision, which was undertaken whenever possible.[15] Individuals with submucous fibrosis were treated symptomatically, and those with confirmed oral cancers were referred to treatment with surgery, radiotherapy, or chemotherapy.

We obtained information on the frequency of oral cancer cases and deaths in both intervention and control groups from the Trivandrum population-based cancer registry, hospital cancer registry of the RCC, and many other sources including medical records departments of the local hospitals, histopathology registers of pathology laboratories, municipal death registers, and death records of churches and mosques. Information was also obtained during house visits and telephone enquiries.
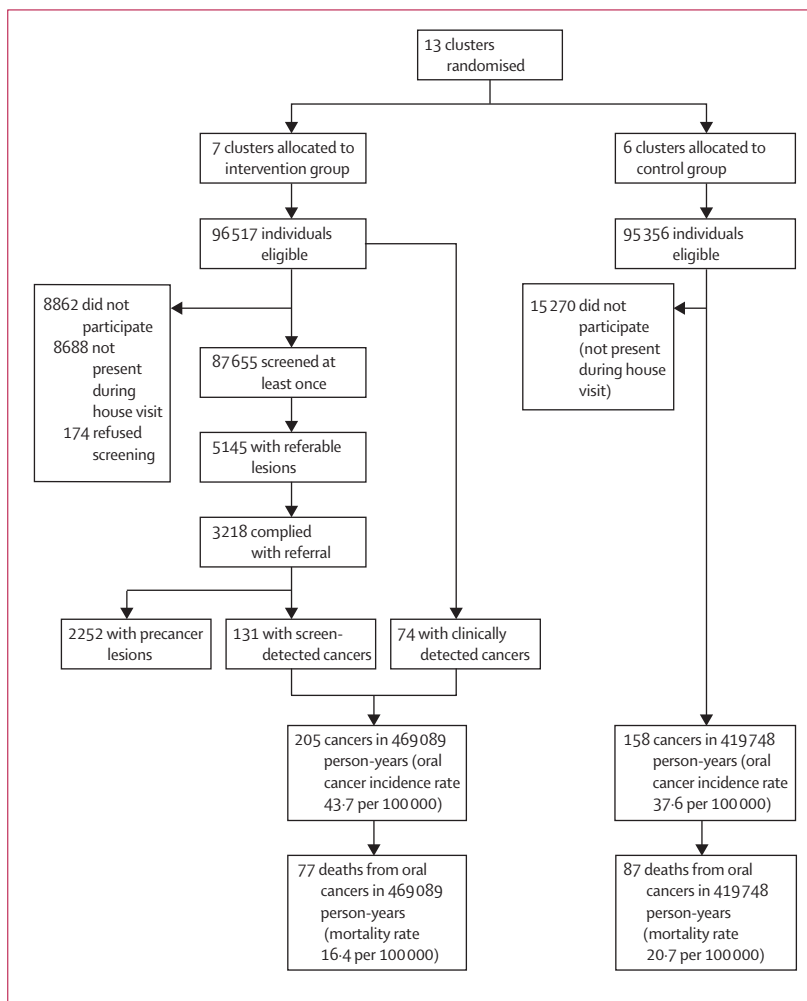

Figure 1: Trial profile of all eligible individuals

We classified instances of oral cancer in the screening group as screen detected (diagnosed during the referral visit after a positive screen); interval (diagnosed after a negative screening test or after a positive screening test when reference investigation was refused); and occurring in non-participants. The staging of oral cancers was done according to the International Union Against Cancer (UICC) TNM (tumour, node, metastasis) staging system.[16] Deaths attributed to oral cancer were defined in patients who had had a previous diagnosis of oral cancer; histologically or clinically confirmed oral cancer; metastatic invasion of lymph nodes, neighbouring tissues, or organs such as the skin; or unresectable disease at death. Three physicians (KR, GT, ST) assessed information on death and were unaware of screening status.

To monitor and assess the study, process measures were used, including participation (proportion of eligible people in the intervention group who had screening), screen positivity (proportion of screened people with a positive screening test), and compliance to referral (proportion of screen-positive people reporting for diagnostic confirmation). Intermediate outcome measures were programme sensitivity (screen-detected oral cancer as a proportion of the total oral cancer cases diagnosed in the intervention group), positive predictive value (proportion of positive screening results with a reference diagnosis of precancer or oral cancer), case fatality (proportion of deaths in oral cancer cases), and survival of oral cancer patients in the screening and control groups. The final outcome measure was oral cancer mortality in the intervention and control groups.

Statistical analysis

Data were entered in D-Base and analysed with STATA version 8.0. Analysis was by intention to treat—ie, all eligible individuals in the clusters randomised were included in analysis irrespective of their participation in the interview or screening. Since this trial used a cluster design, analysis was done with the cluster as the unit of analysis. Comparison of proportions between the study groups was undertaken with a Mann-Whitney non-parametric test based on all cluster summary data. Comparison of rate ratios was done by use of 95% CIs of the rate ratios.[17]

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.[18] For calculation of incidence and mortality rates in all eligible women including non-compliers, the number of person-years in the intervention and control groups was calculated from the date of study entry of the individual to Dec 31, 2004, or death.

The study was planned to have an 80% power at the 5% significance level to detect a 35% reduction in the cumulative mortality rate of oral cancer in 12 years of enrolment between the intervention and the control groups. The death rate from oral cancer in those aged 35 years or older has been estimated at about 20 per 100 000. We have assumed that a cluster with an average of 15 000 people will provide about 110 000 person-years of observation after 9 years (assuming a yearly dropout rate of 5%). With the effect of the intracluster correlation, we assumed a coefficient of variation of 0·15—ie, the true rates of death from oral cancer would vary between 14 and 26 per 100 000 in the control group—which led to a design effect of 1·5 and we thus had to randomise at least six clusters in each treatment group.[19]

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
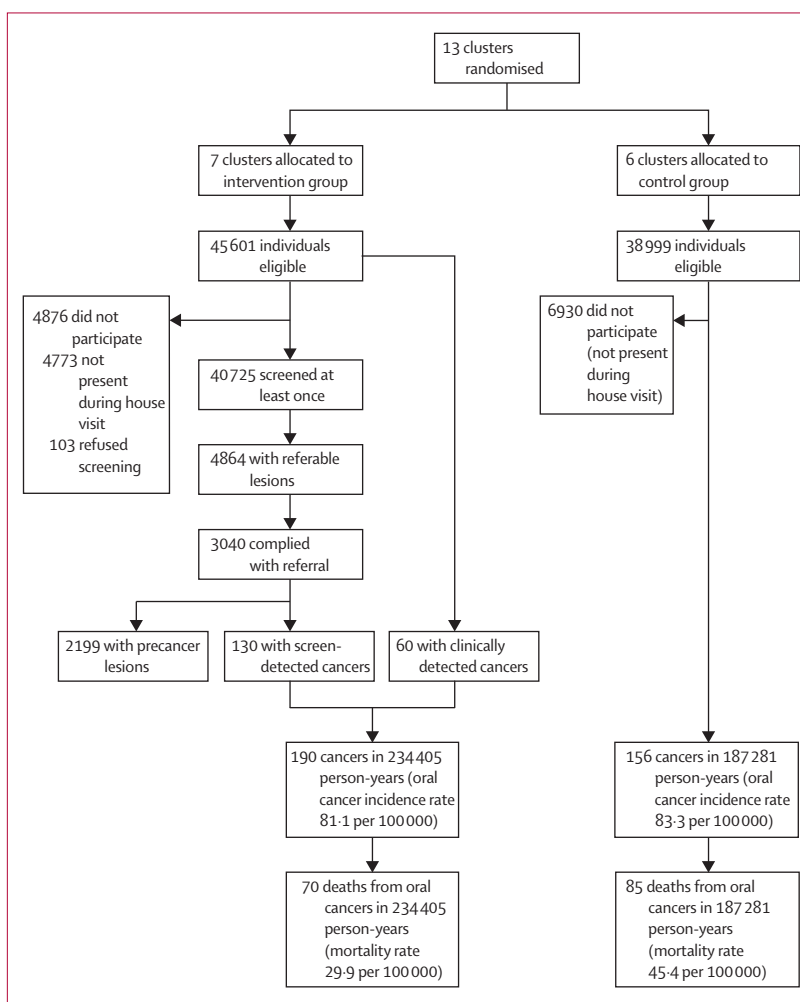

Figure 2: **Trial profile of individuals with tobacco or alcohol habits, or both**

	Intervention group	Control group
Interviewed individuals (number, range)	87 829 (8662–18 389)	80 086 (7334–18 587)
Household		
Type of house (thatched)	34 307 (39%, 31·2–51·2%)	26 997 (35%, 24·1–43·0%)
Income (<1500 rupees [US$35] per month)	42 415 (49%, 14·8–61·1%)	30 849 (40%, 25·8–53·6%)
Individual		
Sex (male)	35 687 (41%, 36·6–43·7%)	31 281 (39%, 35·3–45·7%)
Age (years; mean [SD, range])	49 (0·7, 48–50)	49 (0·8, 48–50)
Religion (Hindu)	59 733 (71%, 32·1–89·4%)	59 807 (72%, 39·4–83·6%)
Occupation (manual worker)	68 645 (78%, 65·5–93·9%)	55 811 (71%, 60·8–82·4%)
Education (schooling)	68 263 (78%, 66·1–87·6%)	64 291 (78%, 63·2–91·9%)

Data are number of individuals (% mean, % range in clusters) unless indicated otherwise. % means are averages of cluster proportions.

Table 1: **Baseline characteristics of eligible individuals who were interviewed**

	Men			Women		
	Intervention (n=41 540)	Control (n=41 954)	p	Intervention (n=54 977)	Control (n=53 402)	p
No habits	10 933 (27%)	13 996 (33%)	0·1531	39 923 (73%)	42 361 (79%)	0·1985
Chewing	12 329 (30%)	10 586 (25%)	0·7751	14 570 (27%)	10 748 (20%)	0·1531
Smoking	26 133 (63%)	23 270 (56%)	0·0455	1610 (3%)	609 (1%)	0·0633
Alcohol	17 738 (43%)	15 472 (37%)	1·0000	133	127	0·1161

Data are number of individuals (%).

Table 2: **Distribution of personal habits by sex and study groups**

Results

Figure 1 shows the study profile with respect to eligible individuals, person-years, oral cancer incidence, and mortality rates, and figure 2 shows the same profile in people at high risk (ie, users of tobacco or alcohol, or both). Of all the eligible individuals, 87 829 (91%) in the intervention group and 80 086 (84%) in the control group were interviewed. The study groups were well balanced as indicated by the similar distribution of age, sex, religion, and socioeconomic status (table 1). The distribution of pan-tobacco chewing and alcohol use in the study groups was similar, but the proportion of smokers was slightly higher in the intervention group (table 2). Tobacco smoking predominantly consisted of bidi (a local cigarette made by wrapping coarse tobacco in a dried temburni leaf) followed by cigarette smoking. The most common alcoholic drinks were toddy (local palm wine) and arrack (brewed from sugarcane juice). Smoking and alcohol use were reported rarely in women.

	Men (n=41 540)	Women (n=54 977)	Total (n=96 517)
Not screened	5941 (14%)	2921 (5%)	8862 (9%)
Screened once	16 744 (40%)	17 599 (32%)	34 343 (36%)
Screened twice	10 274 (25%)	13 936 (25%)	24 210 (25%)
Screened thrice	8581 (21%)	20 521 (37%)	29 102 (30%)
Individuals with referable lesions	2675	2470	5145
Individuals who complied with referral	1604 (60%)*	1614 (65%)*	3218 (63%)*

*% of individuals with referable lesions.

Table 3: **Screening history of individuals invited to screening**

Of the people interviewed and invited for screening in the intervention group, 174 refused. Of those enumerated, 87 655 (91%) were screened at least once, 53 312 (55%) twice, and 29 102 (30%) thrice (table 3). Rate of test positivity was 7·3% in the first round, 2·6% in the second, and 2·1% in the third. Of the 5145 screen-positive individuals, nearly two-thirds complied with referral. Of these individuals, 835 (26%) had healthy mucosa or benign lesions; 2252 (70%) were diagnosed with oral precancerous lesions (lichen-planus [n=51], homogeneous leucoplakia [n=897], non-homogeneous leucoplakia [n=795], and submucous fibrosis [n=509]); and 131 (4%) with invasive oral cancer. The detection rate of oral precancerous lesions and oral cancer in the first, second, and third rounds of screening were 28·0, 11·6, and 11·3 in 1000 screened people, respectively. The positive predictive value of the screening test to detect oral precancerous lesions and invasive cancer was 74%. Of the 2252 individuals with oral precancers, 577 (26%) had biopsies and 201 had histologically confirmed dysplasia.

During 1996–2004, 205 cases of oral cancer (131 screen-detected, 59 interval cancers, and 15 non-participants) were diagnosed in the intervention group and 158 cases in the control group. The programme sensitivity to detect oral cancer was 64% (131 of 205). In the intervention group, the intraoral site distribution of cancers were: lip (four [2%]); tongue (43 [21%]); gingiva (16 [8%]); floor of mouth (seven [3%]); hard palate (14 [7%]); and buccal mucosa (121 [59%]). Site distribution in the control group was: lip (two [1%]), tongue (57 [36%]), gingiva (23 [15%]), floor of mouth (nine [6%]), hard palate (11 [7%]), and buccal mucosa (56 [35%]). Table 4 shows stage distributions of oral cancer cases; 41% of the cases in the intervention group were at stages I or II compared with 23% cases in the control group (p=0·004). A significantly higher 5-year survival rate was recorded in the intervention group than in the control group (50% *vs* 34%; p=0·009).

Table 5 shows the number of person-years, oral cancer cases, deaths, frequency, mortality rates, and rate ratios in all eligible individuals as well as in those with and without tobacco or alcohol habits, or both, in the intervention and control groups. Table 6 presents these values stratified by sex. There were 164 oral cancer deaths in the intervention and control groups. The 21% reduction in oral cancer mortality in all individuals in the intervention group compared with controls was not significant (table 5). However, a significant 34% reduction in mortality was recorded in tobacco or alcohol users in the screening group, compared with controls (table 5).

No significant reduction was seen in oral cancer mortality when stratified by all male or female eligible participants (table 6). However, there was a significant 43% reduction in oral cancer mortality in men with tobacco or alcohol use, or both, in the intervention

group compared with controls; the 22% mortality reduction in women with these habits in the intervention group compared with controls was not significant (table 6).

Discussion

Our results showed that overall, the rate of oral cancer deaths in the intervention group (that was screening for cancer) was non-significantly lower than those in the control group, 9 years after initiation of screening. However, in users of tobacco or alcohol, or both, this value was significantly lower in the intervention group than in controls. Mortality rates were also reduced in users of tobacco or alcohol, or both, in the intervention group compared with controls, although this difference was only significant in male users.

The oral cavity is an easily accessible site for screening by doctors, nurses, and health workers or for self-examination, and visual screening has been shown to detect early oral neoplasia if provided as part of routine medical care by health workers.[5–9,20–22] The sensitivity of oral visual inspection to detect lesions varied from 57·7%–61·4% in previous studies,[5–9,20–22] and the specificity ranged from 98·6 to 98·8%. Early oral cancer cases have a better prognosis than those with advanced disease,[23–25] although no definite evidence so far indicates that organised and systematic, population-based oral screening can reduce mortality from oral cancer.

A similar nationwide oral cancer screening programme has been ongoing in Cuba since 1984,[21] although results have not been definitive. However, a significant reduction in the risk of advanced oral cancer was seen in a case-control study of oral screening in Cuba.[26] Because of the effects of lead time and length bias, the observational data indicating

detection of early stage cancers and the improved survival of early oral cancer cases are not sufficient evidence to recommend organised screening. Evidence of efficacy in the reduction of mortality from

	Intervention group				Control group
	Screen-detected	Interval	Non-responders	Total	
I	40 (31%)	9 (15%)	2 (13%)	51 (25%)	20 (13%)
II	23 (18%)	10 (17%)	1 (7%)	34 (17%)	17 (11%)
III	22 (17%)	12 (20%)	3 (20%)	37 (18%)	35 (22%)
IV	38 (29%)	24 (41%)	5 (33%)	67 (33%)	70 (44%)
Unknown	8 (6%)	4 (7%)	4 (27%)	16 (8%)	16 (10%)
Total	131 (100%)	59 (100%)	15 (100%)	205 (100%)	158 (100%)

Table 4: Stage distribution of oral cancer cases

	Intervention group	Control group	Rate ratio (95% CI)
Overall			
Person-years of observation	469 089	419 748	..
Number of oral cancer cases	205	158	..
Incidence rate (per 100 000)	43·7	37·6	1·16 (0·70–1·92)
Number of deaths	77	87	..
Mortality rate (per 100 000)	16·4	20·7	0·79 (0·51–1·22)
Tobacco or alcohol users, or both			
Person-years of observation	234 405	187 281	..
Number of oral cancer cases	190	156	..
Incidence rate (per 100 000)	81·1	83·3	0·97 (0·66–1·44)
Number of deaths	70	85	..
Mortality rate (per 100 000)	29·9	45·4	0·66 (0·45–0·95)
People with no habits			
Person-years of observation	234 684	232 467	..
Number of oral cancer cases	15	2	..
Incidence rate (per 100 000)	6·4	0·9	7·43 (0·29–192·11)
Number of deaths	7	2	..
Mortality rate (per 100 000)	3·0	0·9	3·47 (0·12– 96·51)

Table 5: Oral cancer incidence and mortality rates in all eligible individuals and eligible individuals with or without tobacco or alcohol drinking habits, or both

	Men			Women		
	Intervention	Control	Rate ratio (95% CI)	Intervention	Control	Rate ratio (95% CI)
Overall						
Person-years of observation	190 926	173 646		278 164	246 102	
Number of oral cancer cases	107	104		98	54	
Incidence rate (per 100 000)	56·0	59·9	0·94 (0·54–1·61)	35·2	21·9	1·61 (1·04–2·47)
Number of deaths	39	55		38	32	
Mortality rate (per 100 000)	20·4	31·7	0·64 (0·38–1·09)	13·7	13·0	1·05 (0·59–1·86)
Tobacco or alcohol users, or both						
Person-years of observation	150 702	128 102		83 703	59 179	
Number of oral cancer cases	99	104		91	52	
Incidence rate (per 100 000)	65·7	81·2	0·81 (0·48–1·35)	108·7	87·9	1·24 (0·83–1·86)
Number of deaths	37	55		33	30	
Mortality rate (per 100 000)	24·6	42·9	0·57 (0·35–0·93)	39·4	50·7	0·78 (0·43–1·42)
People with no habits						
Person-years of observation	40 223	45 544		194 461	186 923	
Number of oral cancer cases	8	0		7	2	
Incidence rate (per 100 000)	19·9	n/a	n/a	3·6	1·1	3·36 (0·14–80·16)
Number of deaths	2	0		5	2	
Mortality rate (per 100 000)	5·0	n/a	n/a	2·6	1·1	2·40 (0·09–61·29)

Table 6: Oral cancer incidence and mortality rates in all eligible individuals and eligible individuals with or without tobacco or alcohol drinking habits, or both, stratified by sex

randomised intervention trials is important for public-health policy decisions on organised cancer-screening programmes, in view of the extensive organisational, technical, and financial inputs that such programmes would demand.

We undertook the study in Trivandrum district, India, because of the high risk of oral cancer[2] and the availability of diagnostic and treatment facilities in the region. No such screening programmes were undertaken anywhere in India and, hence, our study included a control group with access to standard care (ie, no screening) to assess the effect of oral screening compared with the existing care. As a community intervention, clusters were randomised to reduce the potential for contamination between intervention and control groups. However, the number of clusters was rather small for the large population involved; but smaller clusters were not possible in view of the high population density in the study areas (>1000 people per km[2]). Since the study consisted of household counting and personal interviews of the participants, we were able to establish the prevalence of risk factors and the socioeconomic indicators in the study groups. The fact that more than 90% of our screening group was screened at least once and two-thirds of screen-positive individuals complied with referral in our study is encouraging.

In view of the very low risk of oral cancer in people with no tobacco or alcohol use, and such individuals constituted about half the eligible participants in the study, the trial did not have sufficient statistical power to detect a significant decline in mortality in people with no habits, in all eligible individuals as well as in stratified groups of all men and all women. Although screening was not associated with significant reduction in oral cancer mortality in tobacco or alcohol users who were women, case fatality rates were significantly lower than those for controls (38·8% vs 59·3% in all women and 36·3% vs 57·7% in high-risk women; p<0·05). With continued follow-up and accrual of more events, a significant reduction in mortality might be seen in the future in high-risk women as well.

Our findings support the routine use of oral visual screening in the reduction of oral cancer mortality in the high-risk group of users of tobacco or alcohol, or both. This study indicates that oral screening could be restricted to high-risk individuals and organised visual screening is a worthwhile initiative of control for oral cancer in addition to primary prevention efforts to reduce tobacco and alcohol use. We believe that oral screening of high-risk individuals should be established in routine health services in India, in view of the high burden of disease (83 000 new cases and 46 000 deaths yearly) in the country[1,2] and other high-risk areas. On the basis of our findings, oral visual screening has the potential to prevent at least 37 000 deaths from oral cancer worldwide every year.

References
1   Ferlay J, Parkin DM, Pisani P. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. Lyon: IARC Press, 2004.
2   Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer incidence in five continents. Lyon: IARC Press, 2002.
3   IARC monographs on the evaluation of carcinogenic risks to humans. Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines. Lyon: IARC Press, 2004.
4   La Vecchia C, Lucchini F, Negri E, Levi F. Trends in oral cancer mortality in Europe. *Oral Oncol* 2004; **40:** 433–39.
5   Warnakulasuriya KAAS, Ekanayake ANI, Sivayoham S, et al. Utilisation of primary care workers for early detection of oral cancer and precancer cases in Sri Lanka. *Bull World Health Organ* 1984; **62:** 243–50.
6   Warnakulasuriya KAAS, Nanayakkara BG. Reproducibility of an oral cancer and precancer detection program using a primary health care model in Sri Lanka. *Cancer Detect Prev* 1991; **15:** 331–34.
7   Mehta FS, Gupta PC, Bhonsle RB, Murti PR, Daftary DK, Pindborg JJ. Detection of oral cancer using basic health workers in an area of high oral cancer incidence in India. *Cancer Detect Prev* 1986; **9:** 219–25.
8   Mathew B, Sankaranarayanan R, Sunilkumar KB, Binu K, Pisani P, Krishnan Nair M. Reproducibility and validity of oral visual inspection by trained health workers in the detection of oral precancer and cancer. *Br J Cancer* 1997; **76:** 390–94.
9   Mathew B, Wesley R, Dutt SC, Amma S, Sreekumar C. Cancer screening by local volunteers. *World Health Forum*, 1996; **17:** 377–78.
10   Sankaranarayanan R. Healthcare auxiliaries in the detection and prevention of oral cancer. *Oral Oncol* 1997; **33:** 149–54.

11 Sankaranarayanan R, Mathew B, Jacob BJ, et al. Early findings from a community based cluster randomised controlled oral cancer screening trial in Kerala, India. *Cancer* 2000; **88:** 664–673.

12 Ramadas K, Sankaranarayanan R, Jose Jacob B, et al. Interim results from a cluster randomized controlled oral cancer screening trial in Kerala, India. *Oral Oncol* 2003; **39:** 580–588.

13 Mathew B. A guide for health workers on early detection of oral cancer. Trivandrum: Regional Cancer Centre, 1988.

14 Mehta FS, Hamner JE III. Tobacco related oral mucosal lesions and conditions in India. New Delhi: Jaypee Brothers Medical Publishers, 1993.

15 Pandey M, Thomas G, Somanathan T, et al. Evaluation of surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, India. *Oral Oncol* 2001; **37:** 103–09.

16 Hermanek P, Sobin H, eds. TNM classification of malignant tumours. 4th edn. Geneva: Springer-Verlag, 1987: 13–18.

17 Bennett S, Parpia T, Hayes R, Cousens S. Methods for the analysis of incident rates in cluster randomized trials. *Int J Epidemiol* 2002; **31:** 839–46.

18 Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 407–81.

19 Hayes RJ, Bennett S. Sample size calculation for cluster randomized trials. *Int J Epidemiol* 1999; **28:** 319–326.

20 Mashberg A, Barsa P. Screening for oral and oropharyngeal squamous cell carcinomas. *CA Cancer J Clin* 1984; **34:** 262–68.

21 Fernandez Garrote L, Sankaranarayanan R, Lence Anta JJ, Rodriguez Salva A, Parkin DM. An evaluation of the oral cancer control programme in Cuba. *Epidemiology* 1995; **6:** 428–31.

22 Mathew B, Sankaranarayanan R, Wesley R, Krishnan Nair M. Evaluation of mouth self-examination in the control of oral cancer. *Br J Cancer* 1995; **71:** 397–99.

23 Ries LAG, Kosary CL, Hankey BF, Miller BA, Harras A, Edwards BK, eds. SEER cancer statistics, review: 1973–1994. Bethesda, MD: National Cancer Institute, 1997.

24 Sankaranarayanan R, Black RJ, Parkin DM. Cancer Survival in Developing Countries. Lyon: IARC, 1998.

25 Yeole B, Sankaranarayanan R, Sunny L, Swaminathan R, Parkin DM. Survival from head and neck cancer in Mumbai (Bombay), India. *Cancer* 2000; **89:** 437–44.

26 Sankaranarayanan R, Fernandez Garrotte L, Lence Anta J, Pisani P, Rodriguez Salva A. Visual inspection in oral cancer screening in Cuba: a case-control study. *Oral Oncology* 2002; **38:** 131–36.