Evaluation of Screening Strategies for Improving Oral Cancer Mortality: A Cochrane Systematic Review

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Abstract: Worldwide, oral cancer has one of the lowest survival rates. It is well recognized that survival rates are improved if the disease is treated in its early stages. The aim of this study was to assess the effectiveness of screening methods in decreasing the mortality of oral cancer. A systematic review on the effectiveness of oral cancer screening was performed using all publications in MEDLINE, CANCERLIT, EMBASE, and Cochrane CCTR between 1966 and September 2002. The evidence was evaluated using the standardized methodology of the Cochrane Collaboration. The search strategy revealed 1,389 citations. From these, 100 potentially relevant articles were selected for review. However, only one randomized controlled study using visual examination as the method for screening fulfilled the selection criteria. Given the limitation of evidence and the potential methodological weakness in the included study, it is valid to say that there is no evidence to recommend inclusion or exclusion of screening programs for oral cancer using visual examination in the general population. In addition, no robust evidence exists that indicates whether other screening methods including toluidine blue, fluorescence imaging, or brush biopsy are either beneficial or harmful. Further high-quality studies to assess the efficacy and effectiveness of screening are required. Additional investigations aimed at elucidating the natural history of oral cancer and evaluating the effectiveness of prevention and opportunistic screening in high-risk groups are needed. A greater understanding of the genetic basis of oral cancer is an essential prerequisite to the development of molecular markers for screening.

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The term "oral cancer" includes all malignancies arising from the lips, oral cavity, oropharynx, nasopharynx, hypopharynx, and other ill-defined sites within the lip, oral cavity, and pharynx.¹ It has been estimated that more than 30,000 new cases of oral cancer are diagnosed in the United States each year, with approximately 8,000 associated deaths.² In the United Kingdom in 1999, the number of newly diagnosed cases of oral cancer was 3,268 in males and 1,831 in females, and the num-

ber of deaths was approximately 1,600.³ Although globally oral cancer represents an incidence of 3 percent (males) and 2 percent (females) of all malignant neoplasms, it has one of the lowest survival rates—50 percent, within a five-year period.⁴ The World Health Organization reported oral cancer as having one of the highest mortality ratios amongst all malignancies.⁵

Unfortunately, most oral cancers lack early signs,⁶ and despite improvements in diagnostic and

therapeutic modalities, the prognosis of patients with oral malignancies has remained poor. In essence, this poor outcome is related to the majority of patients presenting at an already advanced stage of disease at the time of diagnosis.⁷ Moreover, cancer of the mouth occurs in a region of the body that is generally accessible to physical examination by the patient, the dentist, and the physician.⁸ As with other types of cancer, the key to decreasing the suffering of patients and increasing their survival rate is early detection. As a result, attention has been drawn to the potentially successful role of cancer screening programs.⁹

The UK Working Group on screening for oral cancer and precancer concluded that the most suitable screening for oral cancer and precancer is a thorough and methodical examination in good lighting of the mucosal surfaces of the oral cavity.¹⁰ Since 1960, many studies have focused on the important role of toluidine blue dye as an adjunct to the detection of oral cancer.¹¹⁻¹³ Two emerging advanced technology methods for use in oral cancer screening programs are fluorescent imaging and brush biopsy.^{14,15}

The aim of this study was to systematically review the literature relating to the effectiveness of specific screening techniques for oral cancer in asymptomatic individuals with a view to informing current practice.^{16,17} A secondary objective was to assess the effectiveness of early stage detection and morbidity.

Materials and Methods

The systematic review followed the guidelines contained in the Cochrane Collaboration.¹⁸ It synthesizes the evidence qualitatively and then, only where appropriate, uses quantitative methods.

Articles were eligible if they 1) were designed as a randomized control trial (RCT); 2) described a program providing screening for the early detection of oral cancer or potentially premalignant oral lesions including the following methods: visual screening, toluidine blue, fluorescence imaging, and/or brush biopsy; and 3) included follow-up of at least three years.

The primary outcome considered in this review is oral cancer-specific mortality. Other outcomes considered include incidence of oral cancer or potentially premalignant oral lesions, mortality at three or more years, stage at diagnosis, harms of screening (including adverse outcomes from false positive or false negative result on initial screen), costs, and quality of life.

Articles relevant to the search strategy were identified from searches of MEDLINE, CANCERLIT, EMBASE, and Cochrane CCRCT (Central) databases for the period 1966 to September 2002. The search strategy used terms for three categories—oral anatomical parts, cancer, and screening methods—and was supplemented with a

textword search (Table 1). In addition, hand-searching was performed for the following journals: *British Journal of Cancer*, *British Dental Journal*, *Cancer*, *Cancer Research*, *Community Dental Health*, *Community Dentistry*, and *Oral Epidemiology*. Non-English papers were included. The bibliographies of included articles and relevant review articles were checked for studies not identified through the electronic databases or hand-searched journals. Authors of identified RCTs, personal contacts, and manufacturers were contacted to identify unpublished or ongoing trials.

All studies meeting the inclusion criteria underwent validity assessment, data extraction, and statistics evaluation by two

Table 1. Sets of keywords used in the literature search of MEDLINE, EMBASE, CANCERLIT, and Cochrane CCRCT

{Oral}	{Cancer}	{Screening}
MOUTH	MOUTH NEOPLASMS	MASS SCREENING
LIP	PRECANCEROUS CONDITIONS	visual\$ adj screen\$
GINGIVA	tumor\$ or tumour\$ or cancer\$ or carcinoma\$	tolonium chloride
TONGUE	malignan\$	toluidine blue
OROPHARYNX	dysplasia\$	TOLUIDINES
HYPOPHARYNX		toluidine dye
PALATE		brush biopsy
CHEEK		fluorescent imaging
mouth or lip\$ or tongue\$ or gingiv\$ or oropharynx or palate or cheek\$		prevent\$
		screen\$
		Early detection

Note: The symbol \$ acts as a "wildcard" and matches all words that begin with the string of characters before the \$ symbol.

authors (OK, AMG). The two reviewers undertook the quality assessment of the included trials independently and in duplicate as part of the data extraction process.

The quality of included studies was assessed using four criteria:

1. Randomization and allocation concealment for each trial was coded according to the four ratings below, described in the Cochrane Reviewers' Handbook¹⁸:
 - Clearly adequate: if adequate concealment reported.
 - Possibly adequate: if the random allocation was mentioned but the actual method used to conceal was unclear/not known.
 - Clearly inadequate: if there was mention of inadequate concealment.
 - Allocation concealment not used.
2. Blinding of the outcome assessment:
 - Yes
 - No
 - Not appropriate
3. Completeness of the follow-up (is there a clear explanation for withdrawals and dropouts in each screening group?):
 - Yes
 - No
 - No withdrawals/dropouts
4. The proportion of participants who completed the study was recorded.

Using the four criteria listed above, each study was categorized as: low risk of bias (A), median risk of bias (B), and high risk of bias (C), according to section 6.7.1 of the Cochrane Reviewers' Handbook.

Two reviewers independently extracted data using specially designed data extraction forms. For each included study, the following data were recorded:

- year of publication, country of origin, and source of study funding,
- details of the participants including demographic characteristics and criteria for inclusion,
- details on the type of intervention and comparisons,
- details on the study design, and
- details on the outcomes reported, including method of assessment.

Authors of the included studies were asked to confirm the data extracted.

For dichotomous outcomes, the estimate of effect of an intervention was expressed as relative risks together with 95 percent confidence intervals.

Meta-analysis was attempted only if there were studies of similar comparisons that report the same outcome measures. For continuous outcomes, mean differences and 95 percent confidence intervals were used to summarize the data for each group.

Relative risks were combined for dichotomous data and weighted mean differences for continuous data. Random effects models were performed throughout. For cluster randomized trials, the patient numbers were reduced to an effective sample size as described by Hauck et al.¹⁹

Meta-regression was used to explore effects of the following factors on incidence of oral cancer or potentially malignant oral lesions: level of risk for oral cancer (low, medium, or high risk) and duration of trial. Heterogeneity was assessed by inspection of a graphical display of the estimated treatment effects from the trials along with their 95 percent confidence intervals and by Cochran's test for homogeneity undertaken prior to each meta-analysis. Sensitivity analysis was used to assess robustness of results to trial quality. Funnel plots were used to assess for evidence of bias.¹⁹

Type and frequency of side effects and adverse effects such as false positives or false negatives were tabulated and compared between different studies and designs.

Results

The search of MEDLINE via OVID (1966 to September 2002) revealed 1,389 citations. However, adding the terms of the Cochrane Collaborations sensitive search strategy for randomized controlled trials reduced this number to 427 citations. From these, 100 potentially relevant articles were selected for review. Following the review, only one study conducted in Kerala, India was selected for inclusion.^{20,21}

Searches of EMBASE, CANCERLIT, Cochrane CCTR, Cochrane Specialist Register, and bibliographies of review articles did not reveal any further relevant studies that had not been identified by the MEDLINE search. Similarly, hand-searching for oral cancer screening in the identified journals did not identify any further studies.

Of 100 citations selected for the review, forty-eight described uncontrolled or non-experimental studies,^{11-15,22-64} eight were observational as either epidemiological studies or case-control studies,⁶⁵⁻⁷² thirty-seven were narrative reviews or commentar-

ies,^{10, 73-108} four described controlled clinical trials,¹⁰⁹⁻¹² and three described randomized controlled trials.^{20,21,113} However, these randomized controlled trials did not examine toluidine blue, brush biopsy, or fluorescence imaging as a tool for screening or an adjunct method for screening. The only included RCT concentrated on visual screening for the detection and prevention of oral cancer. It was conducted in Kerala, India and described in three papers.^{20,21,113}

Description of the Included Study

In the Kerala study (Trivandrum Oral Cancer Screening Study), all participants (n=148,905) were apparently healthy residents aged thirty-five years or older living in thirteen clusters in rural areas of Trivandrum city, Kerala, India. Those who were bed-ridden, suffering from open tuberculosis or other debilitating diseases, and/or diagnosed with oral cancer were excluded from the study. In each cluster the number of eligible participants varied from 5,177 to 12,147 (mean 8,815). These clusters were allocated into an intervention cohort (number of clusters=7) and a control cohort (number of clusters=6) by blocked randomization.

The intervention group in the second round of screening consisted of 78,969 persons, 33,540 of whom were male and 45,429 female (Table 2). The participation rate for screening at least once was 88.5 percent: males 81.7 percent and females 93.6 percent. Of the screened subjects, 6.3 percent (n=4,408) had a referable lesion, and 59.7 percent (2,630) of the screen positive subjects complied with referral (Table 3). The control group consisted of 74,739 persons.

Trained and qualified health workers were responsible for carrying out an oral visual inspection. These health workers interviewed the eligible subjects to obtain information by using household information to identify the owner as well as special information related to social and personal habits such as paan and/or tobacco chewing, smoking, alcohol consumption, and dietary supplements. At the same time, the health workers gave advice to those with current tobacco and alcohol habits on giving them up and encouraged others to not initiate these habits.

Intraoral and extraoral examinations were performed in bright daylight with the help of a flashlight. Cervical lymph nodes were palpated. The findings were recorded as normal, nonreferable lesions and referable lesions.

The positively screened participants were examined by dentists or physicians for confirmation. For the confirmed subjects, advice was given to stop tobacco and alcohol habits. In addition, oral biopsies were performed. The intervention and control groups are being followed up. In this study, oral cancer mortality was reported as a major outcome; other outcomes (participation rate, the detection rate of oral precancer and oral cancer, compliance with referral, incidence rate of oral cancers, and characteristics of the oral cancer in the study group) were also measured. The control group clusters were also visited by a "control health worker" who recorded the same sociodemographic information and measured height, weight, blood pressure, and respiratory peak flow measurements. However, the control health workers were not trained in how to undertake a visual oral inspection.

Table 2. Comparison between the intervention and control groups

Study	Intervention Cohort	Control Cohort
Number of Interviewed Participants	n=7 clusters (69,936)	n=6 clusters (60,843)
Gender	27,391 male; 42,545 female	22,933 male; 37,910 female
No Habits	male 7,368 (26.9 percent); female 31,440 (73.9 percent)	male 8,049 (35.1 percent); female 31,010 (81.1 percent)
Chewing Habits	male 8,080 (29.5 percent); female 10,764 (25.3 percent)	male 5,710 (24.9 percent); female 6,748 (17.8 percent)
Smoking Habits	male 17,064 (62.3 percent); female 9,785 (2.3 percent)	male 12,040 (52.5 percent); female 341 (0.9 percent)
Drinking Habits	male 10,271 (37.5 percent); female 85 (0.2 percent)	male 6,971 (30.4 percent); female 38 (0.1 percent)
Participation Rate	male 81.7 percent; female 93.6 percent	-

Table 3. Screening history

Screening History	Male	Female	Total
Not screened	18.4 percent (6,166)	6.4 percent (2,907)	11.5 percent (9,073)
Screened once	48.7 percent (16,334)	41.3 percent (18,762)	44.4 percent (35,096)
Screened twice	32.9 percent (11,040)	52.3 percent (23,760)	44.1 percent (34,800)
Number of subjects with referable lesions	8.4 percent (2,284)	5.0 percent (2,123)	6.3 percent (4,408)
Subjects complied with referral	56.8 percent (1,298)	62.7 percent (1,332)	59.6 percent (2,630)

The study commenced in October 1995, and three rounds of screening at three-year intervals were planned for the study. The first round was completed in May 1998, and the second was completed in June 2002. The principal investigator of this study has confirmed our data extraction to date (Dr. Sankaranarayanan).

Methodological Quality of Included Study

The randomization procedure was conducted using restricted block randomization. Clusters were grouped into blocks of four, and allocation to screening or non-screening group was chosen at random from the six possible combinations available to each block of four. Allocation concealment was not used in this study; this has been confirmed by the author.

In this study, the health workers reported on twenty-four baseline variables including multiple age strata, occupation, education, income, household belongings such as television, and personal habits of chewing, smoking, and drinking. The intervention and control cohorts appear to have been well matched for the stratified variable age at the baseline. However, the distribution of income, education, and household belongings varied in comparability in both study groups at the base line. The distribution of tobacco and alcohol was somewhat different between the study groups. Chewing, smoking, and drinking were greater in the intervention male group than the control group (Table 3). For females, chewing and smoking habits were greater in the intervention group than the control group. However, drinking was similar in the two groups. There were fewer participants with no tobacco or drinking habits in the intervention group for both males and females (Table 3). These differences in the baseline variables might be expected in cluster randomized studies.

Blinding of the outcome assessment was not described in this study. However, because of the na-

ture of the study and the outcomes assessed, it was impossible for some outcomes to be assessed blindly.

Withdrawals and dropouts were not described clearly in this study. The compliance rate in the male group with referable lesions for confirmatory examination by dentists or physicians was 49 percent as opposed to 54.7 percent among the female group at the end of the first round of screening. However, the compliance rate in the second round slightly improved. It was 59.7 percent of all individuals who screened positive, with males at 56.8 percent and females 62.7 percent. Follow-up is still going on to record the results of the screening during the next three years.

The study reported data on oral cancer incidence, disease-specific mortality, and stage at diagnosis after six years' follow-up. Data on quality of life, all cause mortality, and costs were not reported.

Among the 69,896 participants screened in the intervention group, 4,408 (6.3 percent) were found to have referable lesions. Of these, 2,630 (59.7 percent) complied with referral for confirmatory examination. The number of oral precancerous lesions was 1,887 (71.75 percent) and oral cancer 100 (3.8 percent). The detection rates of oral precancerous lesions and oral cancer were 27.0/1000 and 1.4/1000 screened subjects respectively. Examination of the Trivandrum cancer registry recorded 255 patients with oral cancer. One hundred and forty-nine patients were in the intervention group and 106 in the control group. The crude incident rate of oral cancer was 43.3/100,000 pyrs (person-years) in the intervention cohort and 32.2/100,000 pyrs in the control group (Table 4).

There was no statistically significant difference in death rate from oral cancer between the intervention group and control. Over the six-year period, sixty-five of 149 subjects with oral cancer in the intervention group and sixty-two of the 106 cases in the control group died, a six-year case fatality of 43.6 percent and 58.5 percent in the respective groups.

Table 4. Number of oral cancers diagnosed and death associated rate

Kerala Project	Intervention Group	Control Group
Number of oral cancers	149 (male 83, female 66)	106 (male 64, female 42)
Oral cancer deaths	65	62
Total number of participants	78,969	74,739
Crude incidence rate of oral cancer	43.3/100,000 person-years	32.2/100,000 person-years
Case-fatality rate	43.6 percent	58.5 percent
Age-standardized oral cancer mortality rate	21.2/100,000 person-years	21.3/100,000 person-years
Crude death rate from oral cancer	18.9/100,000 person-years	18.8/100,000 person-years

The age-standardized mortality rate associated with oral cancer in the intervention group and control group were 21.2/100,000 pyrs and 21.3/100,000 pyrs respectively (Table 4).

We examined survival by comparing the proportion of patients alive three years after diagnosis. The three-year survival rate was 57.5 percent in the intervention group and 38.8 percent in the control group ($p>0.05$).

The stage distribution of oral cancer cases based on the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) clinical TNM stage was reported. In the intervention group, 37.6 percent of the cases were in stage I or II, as opposed to 18.9 percent of cases in the control group ($p<0.001$). On the other hand, 57.5 percent of cases in the control group were in the stage III or IV versus 42.3 percent of cases in the intervention group. Unknown stage cases were 20.1 percent in the intervention group and 23.6 percent in the control group.

In this study, compliance with scheduled screening averaged 81.6 percent for males and 93.6 percent for females in the intervention group, whereas the overall participation rate was 81.4 percent in the control group.

The program's sensitivity and specificity in detecting oral cancer were 81.5 percent and 84.8 percent respectively. The positive predictive value of prevalence screening for this study was calculated as the number of screen-selected oral cancers as a proportion of total screen positive subjects (confirmed by biopsy), and it was 39.6 percent for oral cancer.

Discussion

Considering the increased rate of oral cancer incidence globally,⁵ the need to decrease the burden

of suffering from oral cancer is crucial. The oral cavity is easily accessible for physical examination.⁸ Many attempts have been made to assess the effectiveness of oral cancer screening in decreasing the mortality associated with oral cancer.^{47,54} Different methods have been used to accomplish screening.^{14,46,62} Unfortunately, most of the studies reporting on screening strategies have been uncontrolled and thus are not included in the present review.

This is the first systematic review of screening strategies on oral cancer reported in the literature based on randomized controlled trials only. However other reviews of effectiveness^{86,97} and test performance⁹² have also been undertaken.

The Canadian task force on preventive health care conducted a review study on the prevention of oral cancer mortality.⁸⁶ Although the review was systematic, no clear indication of the review methodology was described. Moreover, case-control and cohort studies were included in this review without employing clear inclusion and exclusion criteria. This review focused only on visual clinical examination as a mode for screening without mentioning any details of other types of oral screening strategies. The results of their review suggest that for population screening there is fair evidence to specifically exclude screening for oral cancer. For opportunistic screening (high-risk groups could be targeted) during periodic examination, however, there is insufficient evidence to recommend inclusion or exclusion of screening for oral cancer.

A meta-analysis with regard to the test performance of visual examination as a screening method has previously been performed, but this was not undertaken as part of the systematic review.⁹² Clear criteria for inclusion and exclusion were applied. However, the included studies varied in both their study design and circumstances with regard to screening strategy used, population sample, prevalence of dis-

ease in those populations, and personnel undertaking screening and their experience as well as training in performing the screening. The results of this meta-analysis suggest that, although the included studies have considerable heterogeneity, visual screening had a high discriminatory ability to pick up the target disease, especially as the derived sensitivity values ranged from 0.60 to 0.95 and the specificity figures were between 0.94 and 0.99 for most studies conducted around the world.

The Department of Public Health and Epidemiology in the University of Birmingham (UK) conducted a review using toluidine blue method for screening.⁸⁵ This study systematically reviewed the literature on the usefulness of toluidine blue dye as a screening tool for the detection of oral cancer in general dental practice. The results of this review showed that there is no evidence to suggest that toluidine blue was a cost-effective method of picking up oral cancers in a primary care setting. A meta-analysis study was conducted to evaluate the efficacy of screening for oral cancer with toluidine blue.⁹⁷ However, no inclusion and exclusion criteria for the studies reviewed were reported.

The study identified in this review was found to have some methodological weaknesses, some of which are discussed in the article.²¹ First, the main advantage of RCTs is that random allocation to groups allows both known and unknown confounding factors to be distributed evenly. The included study used cluster randomization with panchayats (municipal administrative units in rural areas in India) as the unit of allocation. When relatively few clusters are randomized, the chance of unbalances in baseline characteristics is increased, and such unbalances were apparent in the study. The Kerala project showed that personal habits with regard to drinking, smoking, and paan chewing were greater in the intervention group than in the control. These differences could bias the results as it may be expected there would be a greater incidence of oral cancer in the group with a higher level of smoking/drinking/paan chewing. The authors of the study suggest the possibility of information bias: participants in the intervention group were more forthcoming in reporting their habits because they were being offered screening. In addition to that, there was no clear explanation of dropouts in each treatment group. Furthermore, the low compliance rate of the positive screened subjects (59.7 percent) might affect the validity of the study.

This study did not raise any issues with regard to costs, quality of life, or even the harms of screening from false positive or false negative findings. These factors may influence the results positively or negatively and are important issues to consider when implementing the screening programmes.

Speight et al.¹⁰² reviewed the psychological disadvantages of screening—namely, risks of increased levels of anxiety in individual patients, trauma from a false positive result, distress of a true positive result, and unnecessary investigations. These could be reduced by careful and honest dissemination of information and by educating subjects about risk reduction benefits.

The incidence of oral cancer and potentially premalignant oral lesions, the stage at diagnosis, and specific death mortality for at least three years were clearly described. These reported data provided positive value for this study. Nevertheless, the results of the included study showed that there was no reduction in incidence of or mortality from oral cancer after the introduction of the screening program and the improvement in survival rates with early stage oral cancer were due to lead time and length bias. When evaluating the effectiveness of the early detection and treatment of a condition, the lead time must be subtracted from the overall survival time of screened patients to avoid lead time bias. Otherwise, early detection merely increases the duration of the patients' awareness of their disease without reducing their mortality or morbidity. Numerous cancer-screening procedures were thought to improve survival until lead time bias was addressed.¹¹⁴

Although the Kerala study showed that the sensitivity and specificity of visual examination to detect oral lesions were over 80 percent and similar to other studies,^{40,61} there was no difference in oral cancer mortality after six years of follow-up. This may be explained by a lack in understanding of the natural history of oral cancer and of the effectiveness of treatment. The UK National Screening Committee undertook an assessment of oral cancer screening during 2002-03. The conclusions of the expert group as presented to the committee were: "There is an overwhelming need for more information about the epidemiology and natural history of oral cancer. Greater awareness of the disease amongst all health professionals and standardised referral pathways would facilitate earlier institution of treatment when necessary. The population should be aware of the disease including possible risk factors and early signs

and symptoms.”¹¹⁵ Thus the need to understand the natural history of oral cancer is crucial.

For diagnostic screening, randomized controlled trials are required to provide the most reliable information for decisions in clinical practice. The lack of trials in this field might be attributed to the many possible obstacles, including the duration of follow-up required, the reproducibility of the screening test by the health workers, compliance, cost, and the relatively low incidence of oral cancer in certain countries.

Unfortunately, there are no published randomized controlled trials of brush biopsy, fluorescence imaging, and toluidine blue. Many clinical trials and reports have raised optimistic indications for the prospective role of these methods as adjunctive aids in the early detection of oral cancer,^{50,64,75} but the vast majority of these studies concentrated on the test diagnostic characteristics rather than the use of these tests for screening.

Conclusions

Our results suggest that there is insufficient evidence to recommend inclusion or exclusion of screening for oral cancer using a visual examination in the general population. In addition, there is no evidence for other methods of screening, such as toluidine blue, fluorescence imaging, and brush biopsy, to be either included or excluded. The data need to be supplemented by further randomized controlled trials to provide the highest level of evidence for practice. However, systematic examination of the oral cavity by general dental practitioners or physicians should remain an integral part of their routine daily work. Particular attention should be paid to high-risk individuals.

Given the lack of evidence to support or refute the use of screening programs for oral cancer, further studies using high-quality methodology on the natural history of oral cancer and prevention methods as well as the effectiveness of opportunistic screening in high risk groups are required. Most recently, many studies have suggested that molecular markers could be useful as prognostic and predictive markers for the premalignant oral lesion.¹¹⁶ It is feasible that research in this field may open doors for better understanding and prognostication. The identification of genes involved in oral cancer is an essential prerequisite to the development of molecular markers for screening.

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