Lessons from Trivandrum Oral Cancer Screening Trial

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Prevention, Early Detection, and Treatment of Oral Cancer

- 300 400 cases and 145 300 deaths annually in the world; a third of global burden in India!
- 5-year prevalence of 702,200 cases globally
- 200,000 cases and 112,000 deaths in Low- and Middle-Income Countries (LMICs)
- 5-year survival <40% in most LMICs
- Highly preventable, yet not prevented!

Common cancer pattern of young adult (15-39 years) Chennai (MMTR), 1982-1986 vs. 2012-14

MMTR, Period: 1982-86 **Men : 779**
Cases: 2169 **Women: 1390**

Primary Site	Men		Women		
	CIR	ASR	P Site	CIR	ASR
Lymphomas	3.0	3.0	Cervix	13.1	13.9
Stomach	1.8	1.8	Breast	5.9	6.2
Leukaemias	1.6	1.6	Ovary	2.2	2.3
Brain N.S	1.6	1.6	Stomach	1.5	1.5
Mouth	0.9	0.9	Lymphomas	1.3	1.3
All sites	19.1	19.0	**All sites**	36.2	37.8

MMTR, Period: 2012-2014 **Men : 847**
Cases: 1902 **Women: 1055**

Primary Site	Men		Women		
	CIR	ASR	P Site	CIR	ASR
Mouth	**3.6**	**3.0**	Breast	9.8	8.1
Tongue	**3.5**	**2.9**	Ovary	2.9	2.8
Leukemias	3.3	3.2	Cervix	2.7	2.2
Lymphomas	2.6	2.7	Lymphomas	2.5	1.5
Brain	2.3	2.0	Leukemias	2.3	2.3
All sites	27.3	24.0	**All sites**	33.0	29.4

Fig. 2: Changing common cancer pattern in sub-groups of young adult men Chennai, 1982-86 vs. 2012-14

15-29 Age group Men

Lymphomas
- 3.1 Leukaemias
- 1.7 Brain& NS
- 1.3 Bone
- 0.9 Connective & STS
- 0.8 **All sites**

13.1

1982-86

30-39 Age group Men

Stomach
- 4.0 Lymphomas
- 3.0 Brain& NS
- 2.4 Mouth
- 2.3 Leukaemias
- 1.5 **All sites**

31.0

15-29 Age group Men

Leukaemias
- 2.7 Tongue
- 2.2 **Mouth**
- **2.2** Lymphomas
- 2.0 Brain& NS
- 1.6 **All sites**

19.0

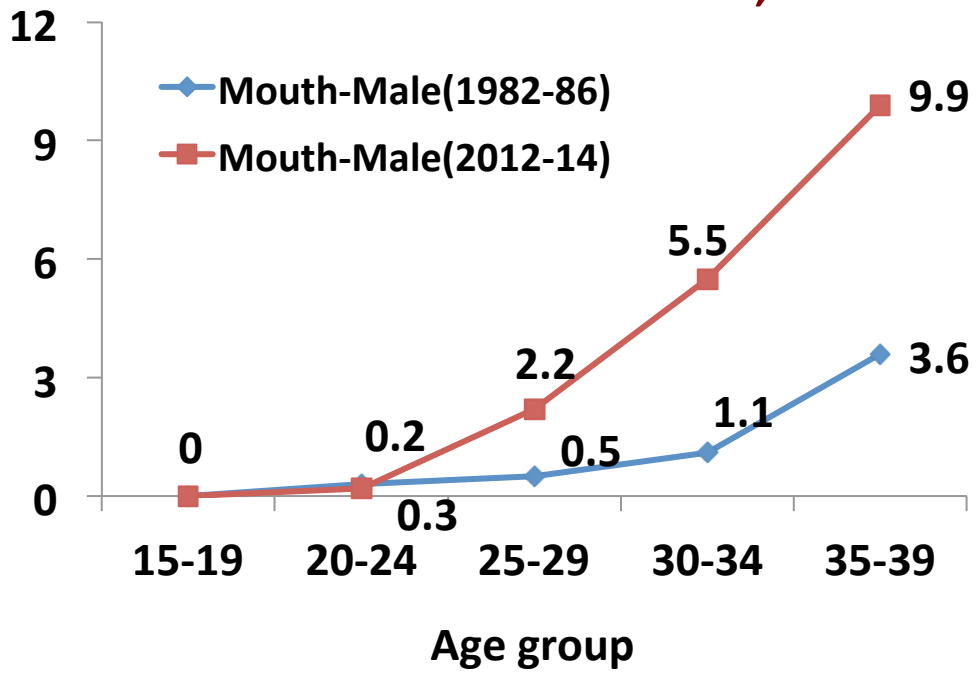
2012-14

30-39 Age group Men

Mouth
- **9.9 Tongue**
- **9.8** Leukaemias
- 3.6 Brain& NS
- 3.1 Stomach
- 2.8 **All sites**

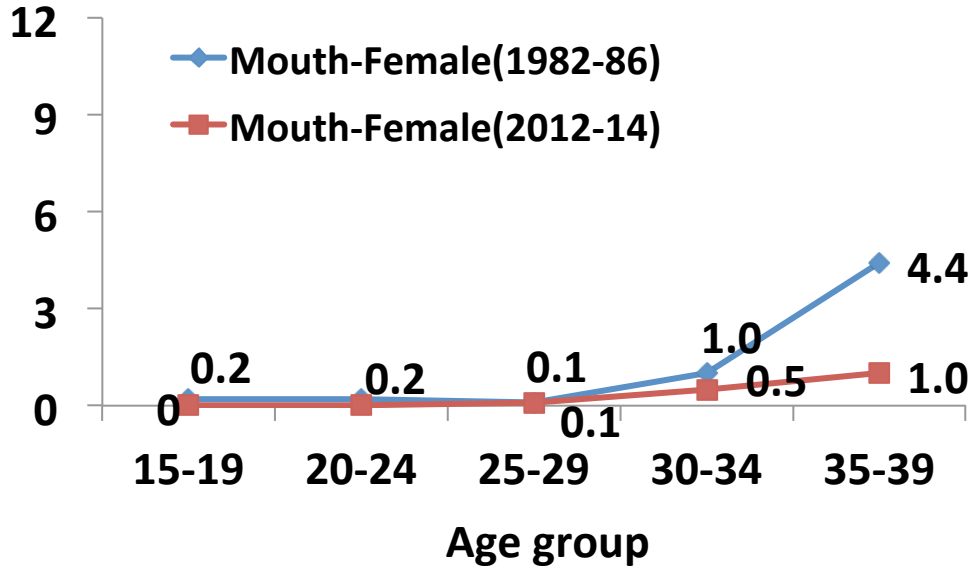
52.8

Trend in age-specific rates of mouth cancer among young adult men Chennai, 1982-1986 vs. 2012-14



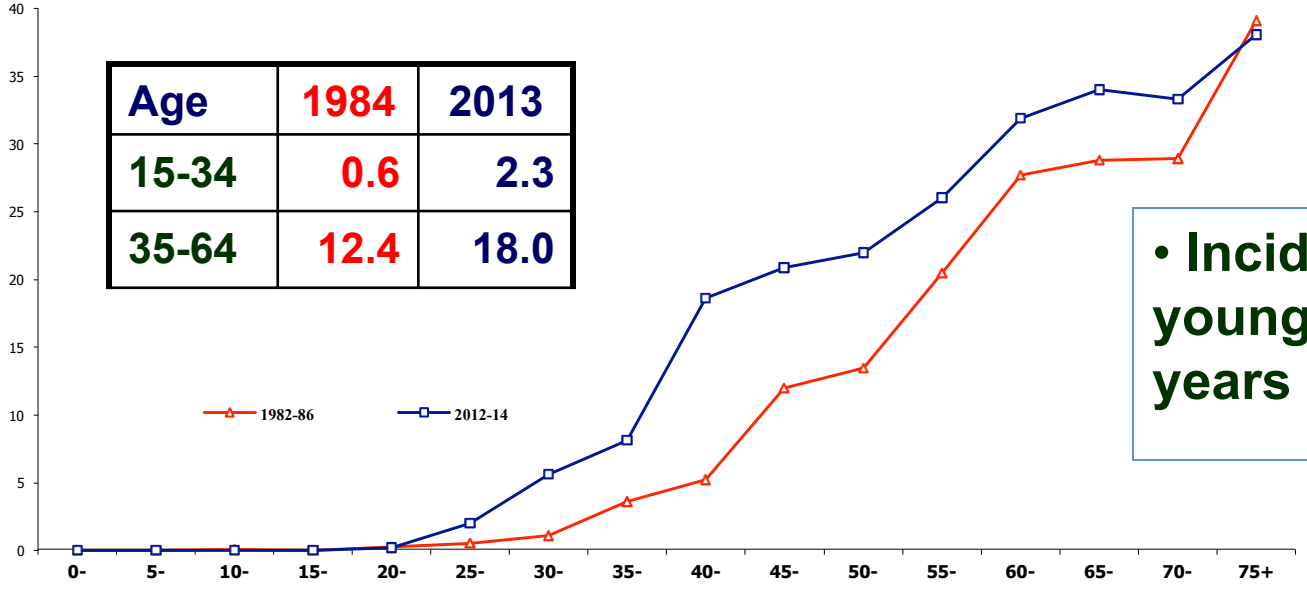
Rate ↑ among young adult men in 2012-14 compared to 1982-86

Rate ↓ among young adult women in 2012-14 compared to 1982-86



Trend of age-specific incidence rate, Mouth cancer, Chennai, 1982-86 vs. 2012-14

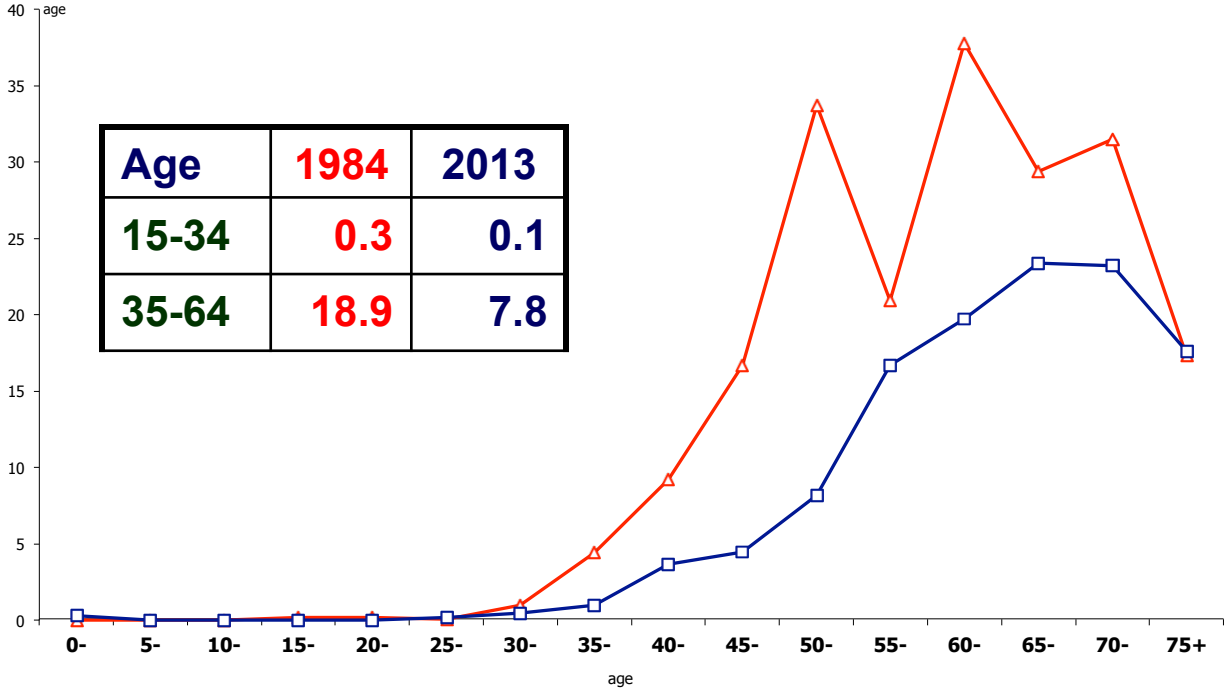
Age	1984	2013
15-34	0.6	2.3
35-64	12.4	18.0



- Incidence rate ↑ in young adults in recent years among men

- Incidence rate ↓ in young adults in recent years among women

Age	1984	2013
15-34	0.3	0.1
35-64	18.9	7.8



Early detection tests for oral neoplasia

- Physical (visual) examination of the oral cavity
- Mouth self-examination (MSE)
- Oral exfoliative cytology
- Toluidine blue intravital staining
- Oral brush biopsy (oralCDX Brush test)
- Chemiluminesence (viziLite system)
- Tissue fluorescence imaging
- Tissue fluorescence spectroscopy

Visual (physical) examination of the oral cavity

- Most widely evaluated early detection test
- Simple, affordable
- Providers can be rapidly trained
- Integral part of physical examination, yet not integrated!
- Acceptable sensitivity (58-94%) and specificity (94-99%)
- Positive predictive value 10-30%
- Evidence from descriptive, observational and experimental studies
- Misses cancer in apparently healthy looking area!

Mehta et al., Cancer Detect Prev. 1986;9(3-4):219-25.
Mathew et al., Br J Cancer. 1997;76(3):390-4.
Warnakulasuriya et al., Bull World Health Organ. 1984;62(2):243-50.

Objectives

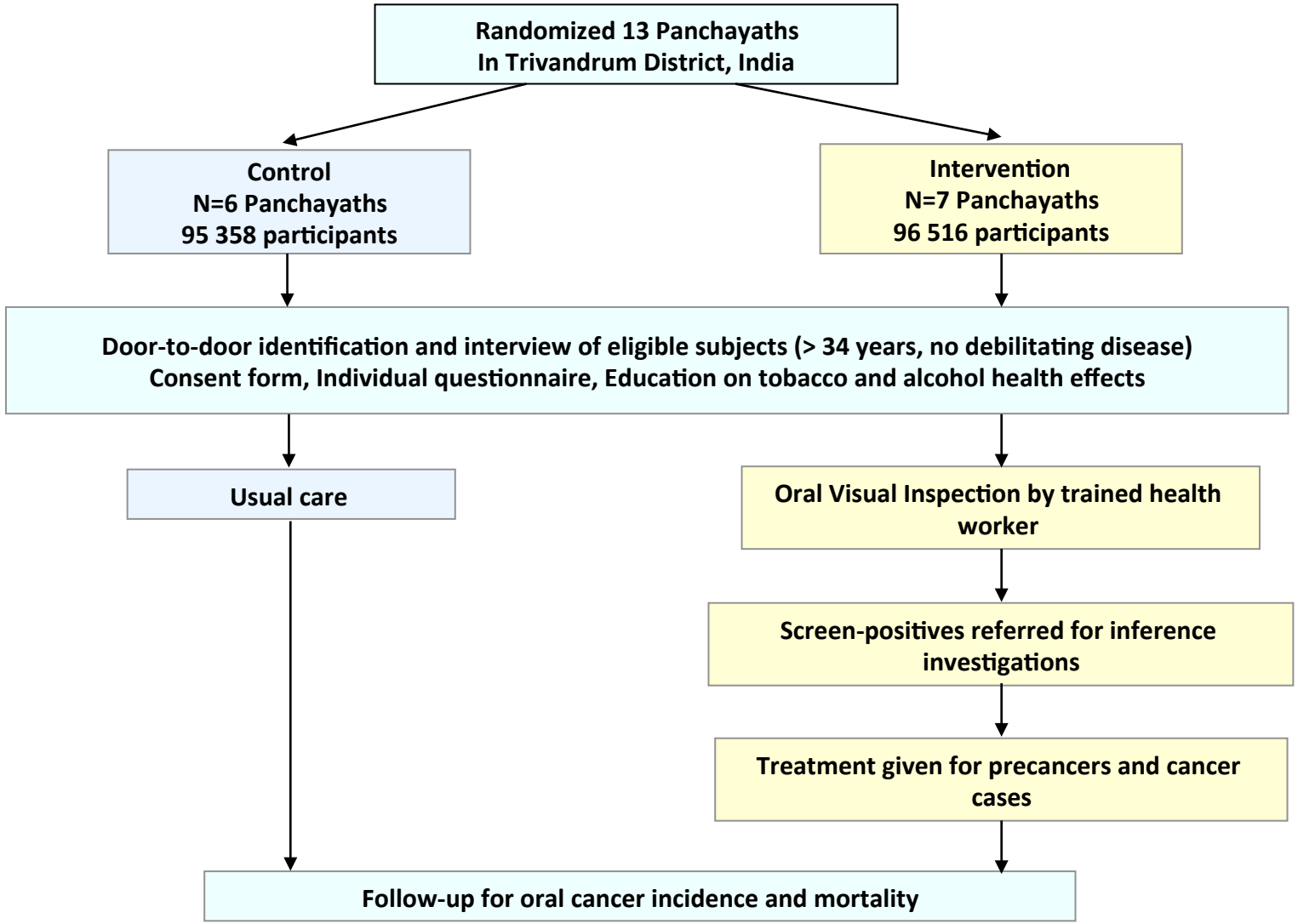
- Evaluate the efficacy and cost-effectiveness of oral cancer screening by visual inspection of the oral cavity in detecting early stages of oral cancer and in reducing mortality
- Study the determinants of population compliance for intervention

A collaborative project of
Regional Cancer Centre (RCC), Thiruvananthapuram, India
and WHO-IARC, Lyon, France

Supported by Association for International Cancer Research (AICR), UK

TRIVANDRUM ORAL CANCER SCREENING STUDY (TOCS)

Randomized controlled trial evaluating the efficacy of oral visual screening in reducing oral cancer mortality (Trivandrum district, India)



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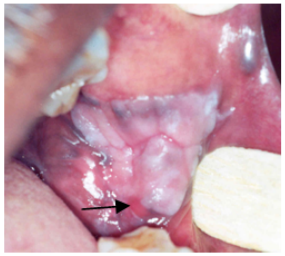
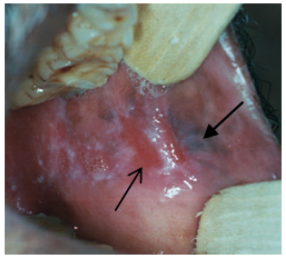
Quick Clinical Reference Chart for Visual Inspection of the Oral Cavity to Detect Precancerous Lesions and Invasive Cancers

Regional Cancer Centre (RCC), Trivandrum, India

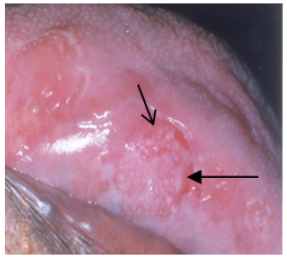
World Health Organization (WHO)
International Agency for Research on Cancer (IARC)



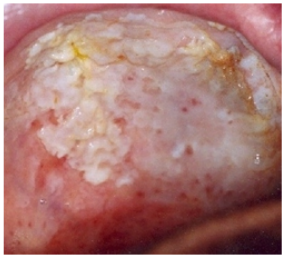
Homogeneous leukoplakia with central fissuring in the left buccal mucosa.



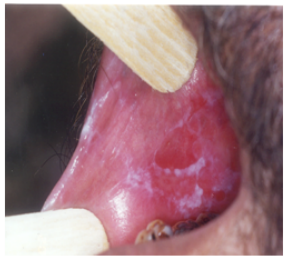
Non-homogeneous leukoplakia (ulcerated leukoplakia) left buccal mucosa with an ulcerated area in the centre (thin arrow) surrounded by white patches and note the tobacco induced pigmentation anteriorly (thick arrow).



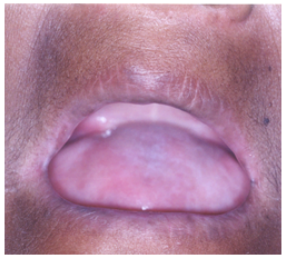
Non-homogeneous leukoplakia (nodular leukoplakia) right margin of the tongue: note the white nodules (thin arrow) on an erythematous base (thick arrow).



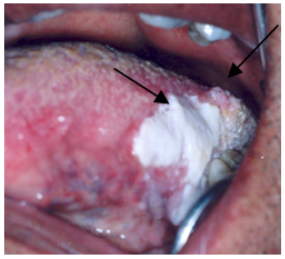
Non-homogeneous leukoplakia (verrucous leukoplakia) hard palate: a diffuse white patch can be seen involving the left and middle portions of the hard palate with warty projections.



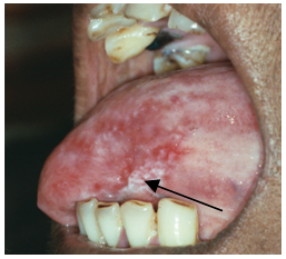
Erythroplakia right buccal mucosa: note the red, velvetty oval lesion



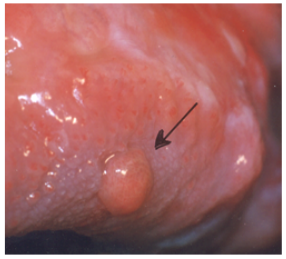
Restricted mouth opening in a patient with oral submucous fibrosis (SMF); note the blanching and extensive depapillation of the tongue.



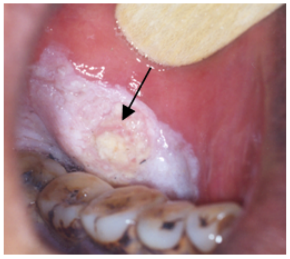
Homogenous leukoplakia on the right lateral margin of tongue from which a proliferative growth is seen arising posteriorly; biopsy from this area confirmed the presence of a well differentiated squamous cell carcinoma.



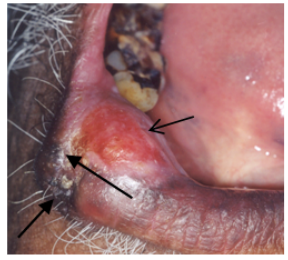
Ulcerated leukoplakia left lateral margin tongue with nodular areas which biopsy showed squamous cell carcinoma.



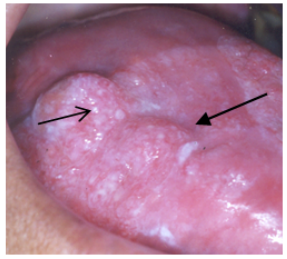
Nodular leukoplakia in the left lateral margin of the tongue harbouring a proliferative growth.



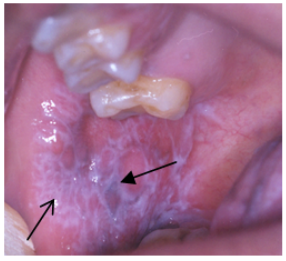
Verrucous leukoplakia with invasive oral cancer at the centre of the lesion (arrow) where a growth can be appreciated, indicating malignant transformation of the leukoplakia.



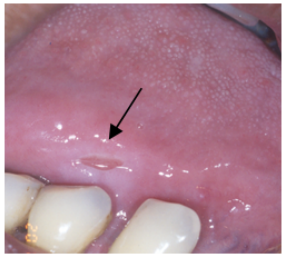
Erythroplakia of the lower lip: note the crusting extending to the vermillion border (thick arrows), which on biopsy revealed well differentiated squamous cell carcinoma.



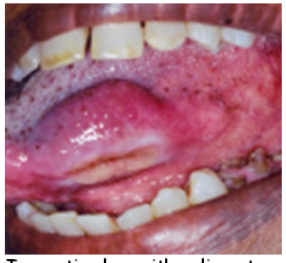
Submucous fibrosis of the tongue with surface nodularities (thin arrows) and multiple, proliferative surface growths (thick arrows) which on biopsy showed well differentiated squamous cell carcinoma.



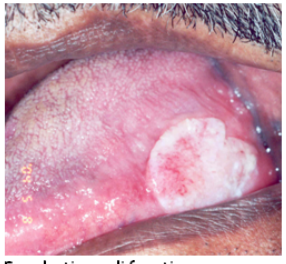
Lichen planus in the right buccal mucosa: note the annular rings (thin arrow) with raised white Wickham's striae (thick arrow).



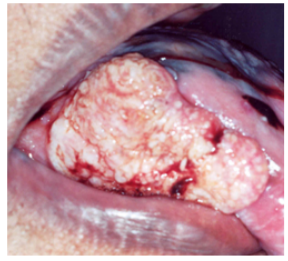
Traumatic ulcer (arrow) in the right lateral margin of tongue caused by irritation of the dorso - lingual cusp of the mandibular canine teeth.



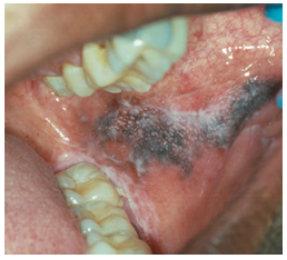
Traumatic ulcer with malignant transformation left lateral margin tongue: note the ulcerative lesion with rolled out borders caused by chronic irritation from the root stumps of the left mandibular 2nd premolar and 1st molar teeth.



Exophytic proliferative growth in the left lateral margin of the tongue: note the co-existing depapillation of the tongue.



Advanced, ulceroproliferative invasive oral cancer in the right lateral margin of the tongue: note the co-existing submucous fibrosis.



Malignant melanoma left buccal mucosa: note the hyperpigmented patch with nodular areas.

Cost-effectiveness of Visual Screening for Oral Cancer in India

Results from the Trivandrum Oral Cancer Screening Study (TOCS) (1996-2004)

	Intervention group	Control group	
Person-years of observation	469 090	419 748	
No. of oral cancers/deaths	*205/77*	*158/87*	
Mortality rate (per 100,000)	16.4	20.7	Rate Ratio: 0.79 (0.51-1.22) 95% CI
Mortality rate among tobacco and/or alcohol users (high-risk individuals)	**29.9**	**45.4**	**Rate Ratio: 0.66 (0.45-0.95) 95% CI**
Cost per cancer detected (intervention compared to control)			
All individuals	-	-	$ 6,228
High-risk individuals	-	-	$ 9,394
Cost per life year saved*			
All individuals	-	-	$ 457
High-risk individuals	-	-	$ 156
* GDP per Capita for India (2004) $ 2900			

Sankaranarayanan et al., 2005: Lancet 365:1927-33
Subramanian et al., 2009: Bull WHO 87:200-206

Supported by Association for International Cancer Research (AICR), UK

Results after 14 years of follow-up (1996-2009)

	All Participants	
	Intervention (895 310 PYO)	**Control (898 280 PYO)**
Oral cancer cases	279	244
Incidence hazard ratio (95% CI)	1.14 (0.91-1.44)	
Stage 3 or worse oral cancers	147	159
Incidence hazard ratio (95% CI)	**0.92 (0.72-1.17)**	
Oral cancer deaths	138	154
Mortality hazard ratio (95% CI)	**0.88 (0.69-1.12)**	

Sankaranarayanan et al., 2013: Oral Oncology 49:314-321

Supported by Association for International Cancer Research (AICR), UK

Results after 14 years of follow-up (1996-2009)

	Tobacco/alcohol users	
	Intervention	**Control**
	(429 620 PYO)	**(377 350 PYO)**
Oral cancer cases	254	232
Incidence hazard ratio (95% CI)	0.97 (0.79-1.19)	
Stage 3 or worse oral cancers	138	154
Incidence hazard ratio (95% CI)	**0.79 (0.65-0.95)**	
Oral cancer deaths	129	147
Mortality hazard ratio (95% CI)	**0.76 (0.60-0.97)**	

Sankaranarayanan et al., 2013: Oral Oncology 49:314-321

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Oral cancer *mortality rate* by number of times screened among all participants (1996-2009)

No. of times screened	Deaths	Person-years of observation	Mortality rate per 100 000 PYO	Mortality hazard ratio* (95% CI)
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)**

Sankaranarayanan et al., 2013: Oral Oncology 49:314-321

Supported by Association for International Cancer Research (AICR), UK

Oral cancer *mortality rate* by number of times screened among tobacco/alcohol users (1996-2009)

No. of times screened	Deaths	Person-years of observation	Mortality rate per 100 000 PYO	Mortality hazard ratio* (95% CI)
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)**

Sankaranarayanan et al., 2013: Oral Oncology 49:314-321

Supported by Association for International Cancer Research (AICR), UK

Proportion of localized (stages I and II) cancers among screened subjects (1996-2009)

Non participants	3/19	(16%)
Screened once	19/78	(25%)
Screened twice	26/66	(32%)
Screened thrice	34/71	(48%)
Screened four times	32/43	(74%)

Sankaranarayanan et al., 2013: Oral Oncology 49:314-321

Supported by Association for International Cancer Research (AICR), UK

Regression, persistence and progression of oral precancerous lesions in a population based study in Trivandrum district, India, 1995-2010

Lesion	Total number	Regressed (%)	Persisted (%)	Progressed to cancer (%)
Homogeneous leukoplakia	1505	1189 (79.0%)	290 (19.3%)	27 (1.7%)
Non-homogeneous leukoplakia	1119	847 (75.7%)	229 (20.5%)	42 (3.8%)
Submucous fibrosis	510	296 (58.0%)	183 (35.9%)	31 (6.1%)

- 64/26,119 (0.2%) people with tobacco/alcohol habits but with no lesions at baseline developed oral cancer in this period
- 11/34,316 (0.03%) people without habits and without lesions at baseline developed oral cancer during this period

Stage distribution among oral cancers diagnosed in oral precancerous lesions in a population based study in Trivandrum district, India, 1995-2010

Lesion	Total cancer cases	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	Stage unknown (%)
Homogeneous leukoplakia	27	9 (33.3%)	3 (11.1%)	4 (14.8%)	11 (40.7%)	0
Non-homogeneous leukoplakia	42	11 (26.2%)	7 (16.7%)	11 (26.2%)	12 (28.6%)	1 (2.4%)
Submucous fibrosis	31	10 (32.3%)	8 (25.8%)	2 (6.5%)	11 (35.5%)	0

- 11/64 (17.2%) in stage I, 13/64 (20.3%) in stage II, 14/64 (21.3%) in stage III, 22/64 (34.4%) in stage IV, and 4/64 (6.3%) in stage unknown among people with tobacco/alcohol habits but with no lesions at baseline developed oral cancer in this period
- 4/11 (36.4%) in stage I, 3/11 (27.3%) in stage II, 2/11 (18.2%) in stage III, 1/11 (9.1%) in stage IV, and 1/11 (9.1%) in stage unknown among people without habits and without lesions at baseline developed oral cancer during this period

Malignant transformation in 5071 southern Taiwanese patients with potentially malignant oral mucosal disorders

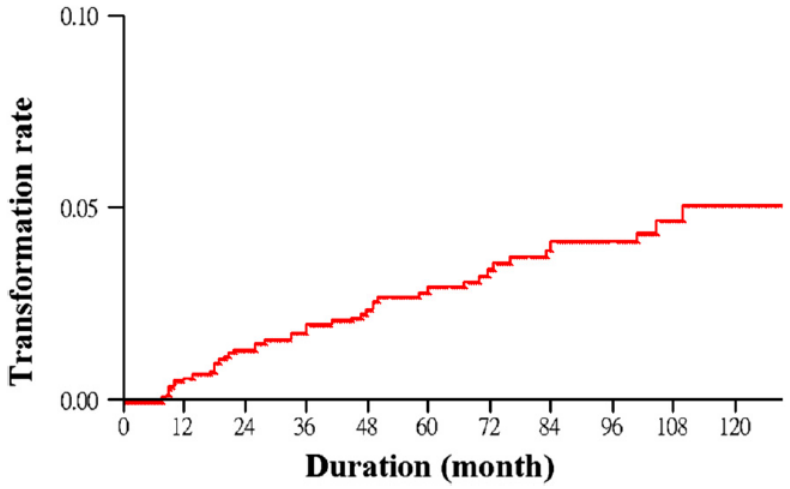

Figure 1 The annual malignant transformation rate of the current study.

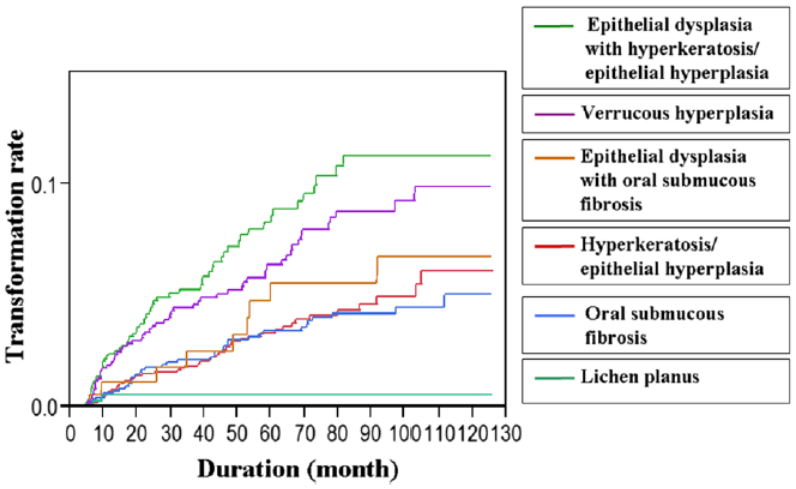

Figure 2 The annual malignant transformation rate of oral potentially malignant disorders ($p < 0.0001$; log-rank test).

Wang et al., BMC Oral Health. 2014;14:99.

Lesson 1: Oral cancer screening

- Oral visual screening is a suitable screening test
- Users of tobacco or alcohol or both are suitable target population for screening
- Oral cancer rare among non-habituees (3/100000 vs 63/100,000 in habituees)
- Oral visual screening leads to earlier detection of oral cancers and reduced oral cancer mortality
- Oral cancer screening is a cost-effective intervention
- It is a feasible intervention that can be readily integrated in health services, but needs proper implementation with trained providers, monitoring and evaluation

Lesson 2: Natural history of oral cancer

- Tobacco and alcohol exposure are major risk factors; HPV as a causal agent in oral cancer is negligible
- Invasive cancer preceded by clinically detectable precancerous lesions: leukoplakia, erythroplakia, SMF (rarely from Lchen planus)
- Field carcinogenesis: the entire exposed oral mucosa is potentially carcinogenic warranting surveillance for second primary cancers
- A high tendency for regional spread and metastasis to cervical lymph nodes
- Limited potential for distant metastasis: none presented with or progressed to distant mets

Lesson 3: Oral cancer screening

- Early diagnosis and prompt Rx improves survival, with good quality of life and reduces mortality from oral cancer
- Staging: Cancers less than 4 cms (stage I and II) with no spread to regional neck nodes are highly curable
- Treatment: Early (particularly stage I) cancers can be cured by single modality Rx, with excellent cosmetics, functional preservation, fewer side effects and good quality of life

Lesson 4: Prognostic factors related to natural history of oral cancer

Disease control difficult when there is involvement/ infiltration of

- Regional lymphnodes (5-year survival <20%)
- Bone/cartilage (5-year survival <10%)
- Muscles (5-year survival <10%)
- Frequency of residual disease high (~60%) in advanced disease even after aggressive multimodality treatment
- Treatment outcomes of residual/recurrent disease are dismal

Lesson 5: Oral visual screening

- High accuracy
- Effective in reducing in incidence and mortality among users of tobacco/arecanut/alcohol
- Easy to integrate in health services

American Dental Association:
Clinical recommendation for oral cancer screening

- Screening by visual and tactile examination to detect potentially malignant and malignant lesions may result in detection of oral cancers at early stages

- Clinicians should remain alert for signs of potentially malignant lesions or early-stage cancers in all patients while performing routine visual and tactile examinations, particularly for patients who use tobacco or alcohol or both

- Clinical confirmation can be sought from a dental or medical care provider with advanced training and experience in diagnosis of oral mucosal disease so as to reduce a false positive or false negative oral cancer screening result

Rethman et al., Tex Dent J. 2012;129(5):491-507.
Richards Evid Based Dent. 2010;11(4):101-2.
the Journal of the America Dental Association's website (http://jada.ada.org/cgi/content/full/141/5/509).

ORAL ATLAS
(http://screening.iarc.fr/atlasoral.php)

Manual prepared by the WHO/IARC and the Regional Cancer Centre, Trivandrum is very useful for training, self learning and quality assurance