

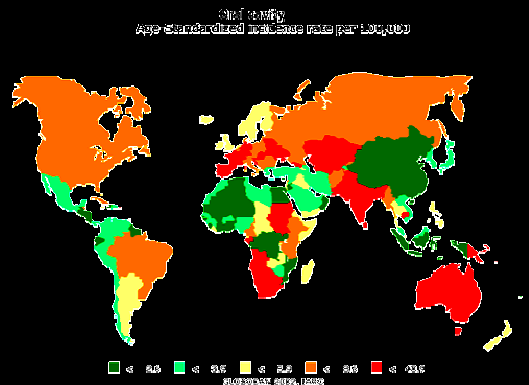
# Preventing Cancers of the Oral Cavity Asian Perspective



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Tata Memorial Hospital  
Mumbai - India

## Oral Cancer Magnitude of the problem

- 300,000 new cases annually ( 2005)
- 2/3<sup>rd</sup> in developing countries
- Most common cancer in males and third common in females
- Some increase in incidence in parts of Europe ,Japan, Australia, New Zealand & USA ( non-whites)

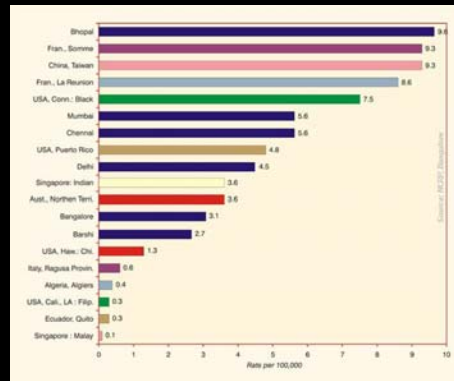


## Oral Cancer AAR International Comparison



**Mouth cancer**

10 - 20% of all cancers



**Tongue cancer**

## Oral Cancer Morbidity & Mortality

- Most common cause of cancer death in most parts of Asia
- Dismal 5 year survival (20 -50 %)
- 145,000 deaths globally, 50,000 in India annually
- Primarily due to late presentation (60-80%)

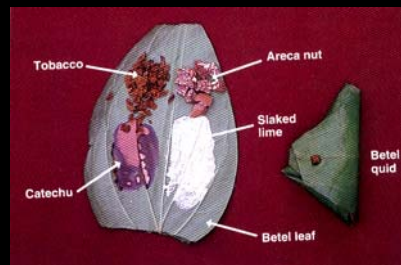
Tata Memorial Hospital  
Of 2275 cases- Only **9%** in Stage I & II

# Battle against Oral Cancer !

- Prevention
- Improved treatment ( no significant change in last 50 years)

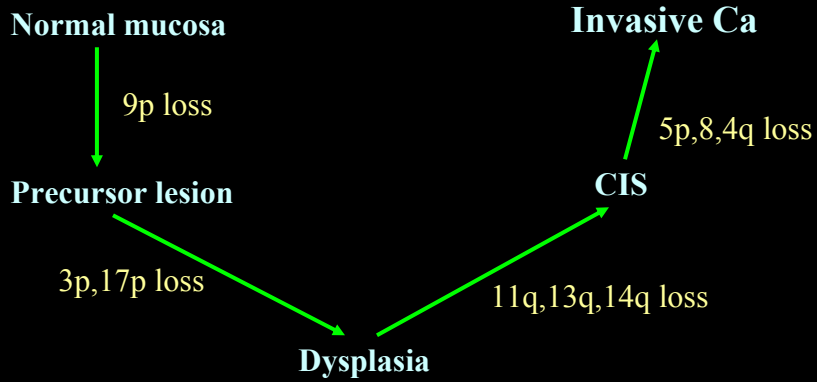
## Oral Cancers Definite Etiology – I

- **Tobacco** (3-12 fold in RR/odds ratio)
- Alcohol
- Dietary factors
- Poor oral / dental hygiene
- Viral - HPV



65 % of men and 33% females in India are addicted to tobacco  
WHO 1997

## Oral Cancers Progression Model-II



## Oral Cancer Well established pre-malignant Lesions- III



5- 20 % of oral leucoplakia will turn malignant

10 -20% of submucous fibrosis will turn malignant

## Oral Cancers Easy Accessibility-IV



Physician  
Self

## Oral Cancer - Prevention

- Primary Prevention
- Secondary Prevention – Early detection

# Primary Prevention

## Cancer prevention- Addressing the etiologic agents

- I- Ban tobacco
- II- Behavioral modifications

### Tough laws & Health education can do wonders!

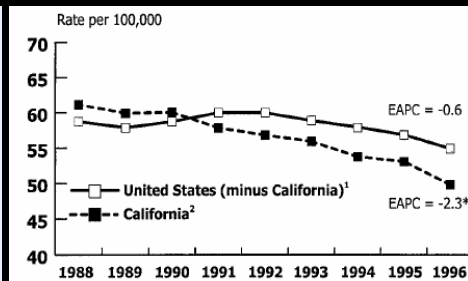
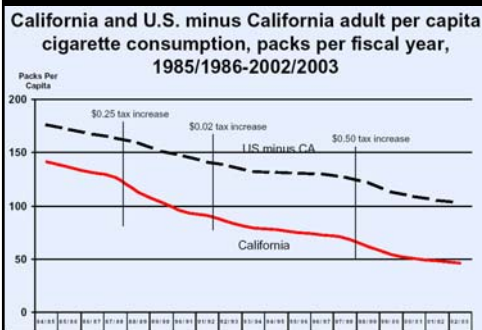


Fig 3. Lung and bronchitis age-adjusted cancer rates. <sup>1</sup>United States (Surveillance, Epidemiology, End Results) includes the following registries:

## Tobacco Ban – Implications

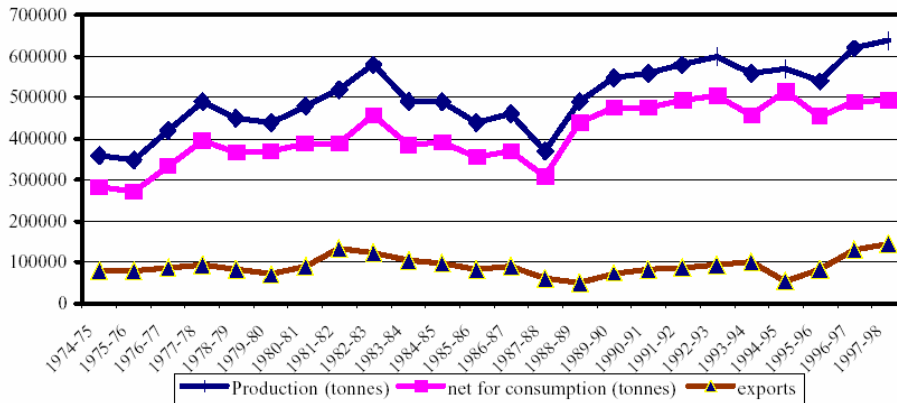
- India 3<sup>rd</sup> largest producer of tobacco
- 900,000 employed in growing and curing industry and 3.4 million in manufacturing
- 97.7 million dollar trade surplus
- Smokeless tobacco \$ 1 billion annually = 0.2 % of the gross national product

***“only industry that has had a constant growth for last few decades”***

## Primary Prevention Ban on tobacco - Initiatives

- Ban on sale, display, manufacture, & distribution in some states
- Tobacco advertising banned on electronic media
- Heavy taxation – 75% of cost of cigarette
- Smoking banned in public places

**Chart III: Tobacco production, exports and net for consumption in India**



Overall lack uniform national policy and implementation

## Primary Prevention-II Tobacco Cessation Intervention study

- >12, 000 tobacco users (3 districts)
- Examined by a dental surgeon
- Counseled by social scientist
- Illustrated books/films/posters

At 1 year

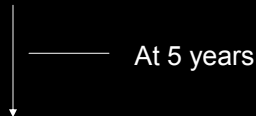
Results:

Tobacco stopped / reduced - 3.1-21.1%  
Regression of precancer  
However, no control gp. for comparison

*Mehta FS; Bull World Health Organ: 1982 -1992*

## ...Primary Prevention Tobacco Cessation Intervention Study

- Identification of a control cohort
- Annual examination of previous gp.
- Additional and continuing educational info (radio broadcasts, newspapers, folk theatre)

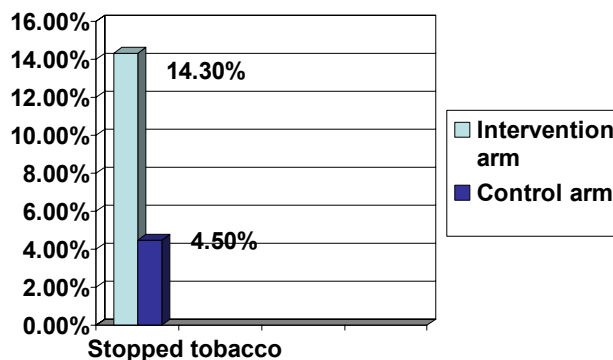


### Results

- Tobacco habits reduced or stopped  
Intervention arm- 33-66%  
Control arm- 12-30%
- Reduction of 5-yr age adjusted cancer incidence

## ...Primary Prevention Tobacco Cessation Intervention Study

After 8 & 10 years



Relapse rates  $\frac{1}{2}$  in intervention group  
Better in subjects with a single habit  
Age adjusted incidence for precancer lower in intervention group

## Primary Prevention ...Conclusions

- Banning tobacco- difficult but useful
- Behavioral modifications
  - do have an impact
  - however, time consuming
  - sustained effort required
- Nonetheless tobacco counseling must be pursued (national & individual)

## Secondary prevention

Early detection of premalignant and malignant lesions

I Screening

II Chemoprevention

## Meta Analysis of measures of performance reported in oral cancer and precancer screening studies

Table 2 Summary of values for expressions of the validity of screening for oral cancer and precancer derived from seven studies

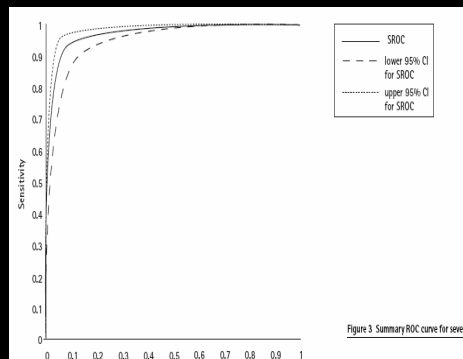
Study and location	Downer et al. (1995) London England	Ikeda et al. (1995) Nagoya Japan	Jullien et al. (1995) (GP) London England	Jullien et al. (1995) (Hosp) London England	Mathew et al. (1997) Kerala India	Mehta et al. (1986) Kerala India	Wamakulasuriya and Pindborg (1990) Sri Lanka
Screened n	309	154	985	1042	2069	1921	1872
Prevalence %	5.50	9.74	2.23	3.07	0.25	1.41	21.63
Sensitivity	0.71	0.60	0.64	0.81	0.94	0.59	0.95
Specificity	0.99	0.94	0.99	0.99	0.98	0.98	0.81
PPV	0.86	0.50	0.64	0.68	0.87	0.31	0.58
NPV	0.98	0.96	0.99	0.99	0.99	0.99	0.98

BRITISH DENTAL JOURNAL VOLUME 192 NO. 6 MARCH 23 2002

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*Moles DR et al, British Dental Journal :2002*

## Results - ROC



BRITISH DENTAL JOURNAL VOLUME 192 NO. 6 MARCH 23 2002

- Pooled sensitivity- 0.796
- Specificity- 0.977 (95% CI- 0.941-0.991)
- Although, heterogeneous,
- High discriminatory ability to pick relevant lesions
- Uniformity of results

## Secondary Prevention Reliability of health workers

- 282 health workers
- Counseling & oral examination
- Initial 3yr period- no difference compared to cancer registry findings
- However, findings of health workers and physicians co-related well  
(sensitivity 94.3%, specificity 99.3%)

*Mathew B et al; Oral Oncol Eur J Cancer: 1995*

### Evaluation of surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, India

M. Pandey<sup>a,\*</sup>, G. Thomas<sup>a</sup>, T. Somanathan<sup>a</sup>, R. Sankaranarayanan<sup>b</sup>, E.K. Abraham<sup>a</sup>, B.J. Jacob<sup>a</sup>, B. Mathew for the Trivandrum Oral Cancer Screening Study Group<sup>1</sup>

Intervention arm  
n= 59,894

↓  
Premalignant lesions  
n=1310 (2.1%)

↓  
Leukoplakia  
n=1154

↓  
Total biopsies- 297  
Excised- 76

↓  
**Cancer- 35 patients**


## Screening for early detection and prevention of oral cancer

### Cochrane Review

- 112 citations found
- 51 uncontrolled trials
- 10 observational studies
- 6 RCTs- but 5 did not meet selection criteria (end point not mortality)
- 1 RCT reviewed

*Kujan O, The Cochrane Collaboration 2007 Issue 1*

## Screening Visual Oral Examination.

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

Rengaswamy Sankaranarayanan, Kunnambath Ramadas, Gigi Thomas, Richard Muwonge, Somanathan Thara, Babu Mathew, Balakrishnan Rajan, for the Trivandrum Oral Cancer Screening Study Group

*The Lancet. June 2005, Volume 365, Issue 9475*

# Cluster Randomized Trial

**1996-2004**

## Health worker Examination

N = 96,517  
91% - Once,  
55% - Twice  
30% - Thrice

## Health Education

N= 95,356  
Standard care

5145 screen positive  
63% complied with referral

# Results for the Entire Population

Health Education  
+  
Visual Examination

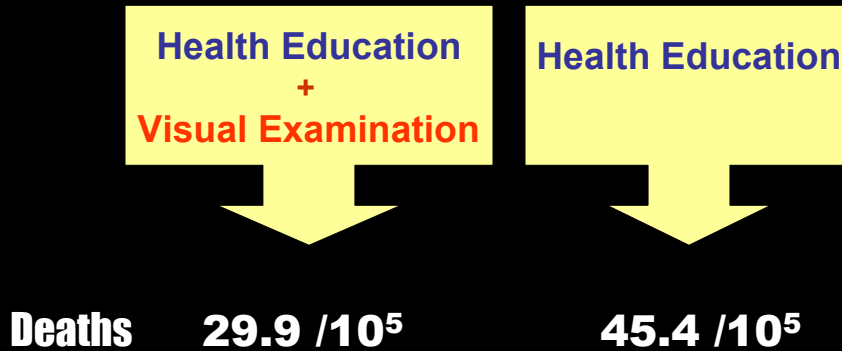
Health Education

Deaths 16.4 / 10<sup>5</sup>

Deaths 20.7 / 10<sup>5</sup>

## Individuals with tobacco / alcohol habits

Mortality ratio **0.66** (95% CI 0.45-0.95)



Potential to save 37,000 deaths worldwide

## Critique

- Lack of concealment
- Small clusters randomized
- Close geographical proximity-contamination
- Low compliance rate of positive screened subjects (63%)

## Cochrane review - Conclusions

- Insufficient evidence to recommend routine screening for Oral cancer with visual inspection
- More RCTs required
- Till then, regular opportunistic screening by visual examination may be effective

- **Role of oral self examination**

- Role of diagnostic aids

## Diagnostic Aids



Cochrane Review

*“No robust evidence for diagnostic aids (toluidine blue, fluorescence imaging, brush biopsy)”*

*Kujan O, The Cochrane Collaboration 2007 Issue 1*

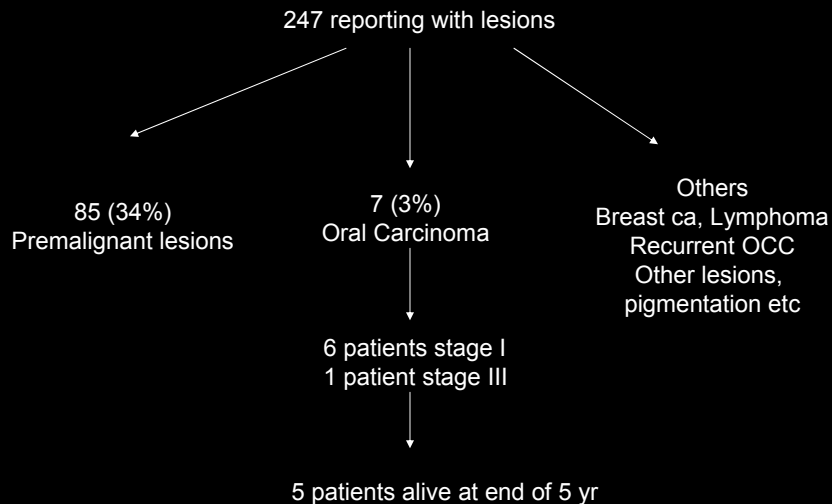


## Mouth Self Examination (MSE)

- Study planned to evaluate feasibility of MSE
- 450 students distributed brochures to 9000 households
- > 30 yrs/ tobacco users
- Eligible subjects- ~ 22,000
- No. practiced MSE- 8028 (36%)
- No. reporting with lesions- 247

*Mathew B et al; Br J of Cancer 1995*

## Mouth Self Examination (MSE) Results



## Mouth Self Examination (MSE)

*Mehta et al-* Detection rates - 51/1,00,000

Present study- 87/1,00,000

*However study shows that educating patients with MSE is feasible*

## Secondary Prevention-II Chemoprevention

**The administration of agents, either biologic or synthetic, to reverse or suppress premalignant changes.**

- Vit. A (Retinoids)
- $\beta$  Carotene (carotenoids)
- Vit C
- Vit E
- Natural agents
- NSAIDS

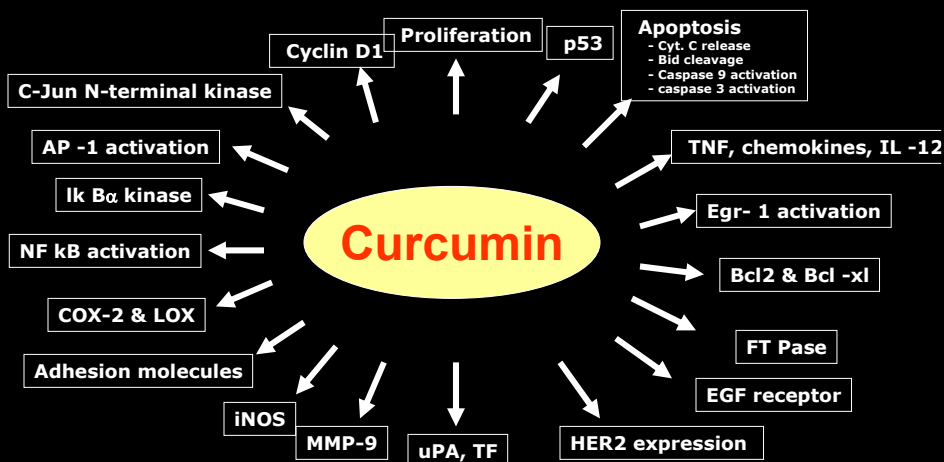
## Chemoprevention Cochrane review 2007

- RCTS with Oral Leukoplakia
- 9 studies – 501 pts.
- 5 retinoid, 2 betacarotene, 1 ketorolac, 1 green tea, 1 bleomycin

# Cochrane Conclusions.....

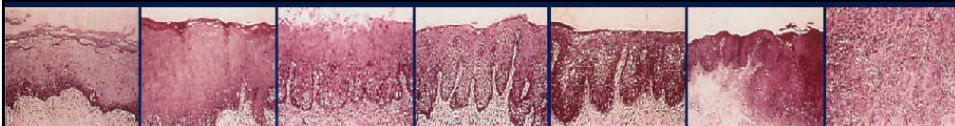
- No difference in malignant transformation
- Response rates in lesions more with retinoids
- Side effects but good compliance
- Lesion return on – stoppage
- Need for further trials with new agents

## Molecular Targets of Curcumin



## Newer trends in prevention Molecular markers

## Limitations of Pathologic Grade



Normal    Hyperplasia    Mild dysplasia    Moderate dysplasia    Severe dysplasia    In situ    Invasive

15% dysplastic  
11-36% of dysplastic lesions convert to CA

Dysplasia is subjective  
Different areas may have different grades of dysplasia

# Molecular Status

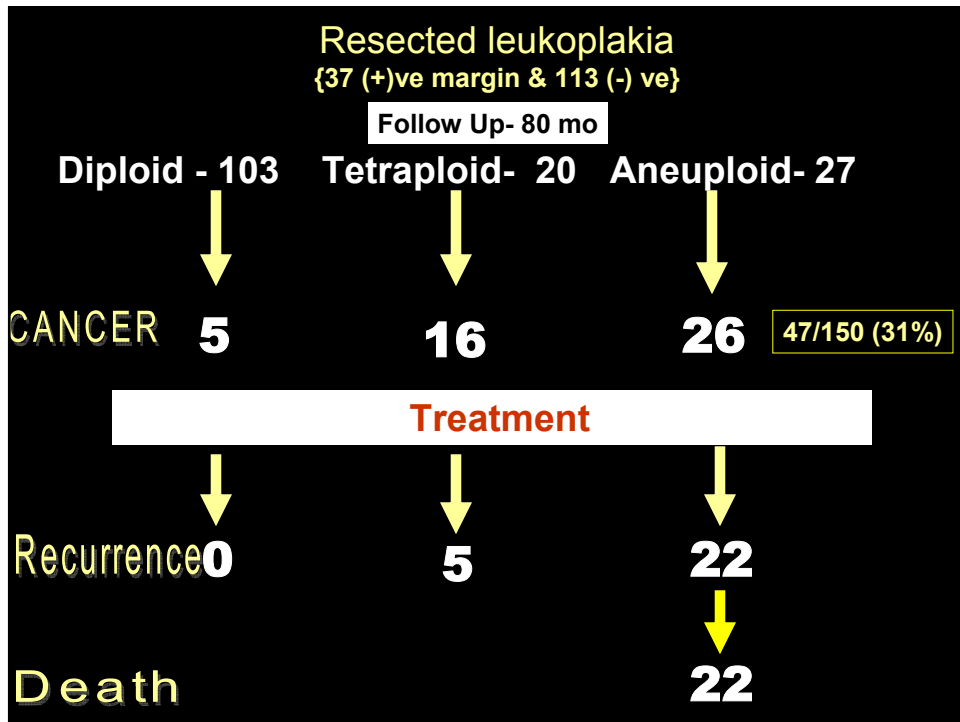
- p53
- RAR $\beta$
- DNA content (aneuploidy)
- TGF $\alpha$
- EGFR
- COX-2
- micronuclei
- chromosome instability -3p, 9p
- C myc oncoprotein

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

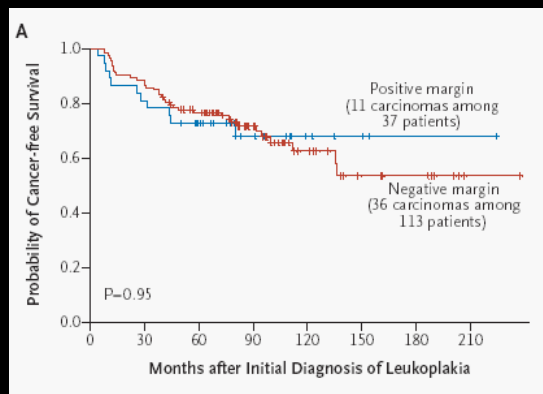
## The Influence of Resection and Aneuploidy on Mortality in Oral Leukoplakia

Jon Sudbø, M.D., D.D.S., Ph.D., Scott M. Lippman, M.D.,  
J. Jack Lee, D.D.S., Ph.D., Li Mao, M.D., Wanja Kildal, M.Sc., Asle Sudbø, Ph.D.,  
Simone Sagen, M.P.H., Magne Bryne, D.D.S., Ph.D., Adel El-Naggar, M.D., Ph.D.,  
Björn Risberg, M.D., Ph.D., Jan F. Evensen, M.D., Ph.D.,  
and Albrecht Reith, M.D., Ph.D.

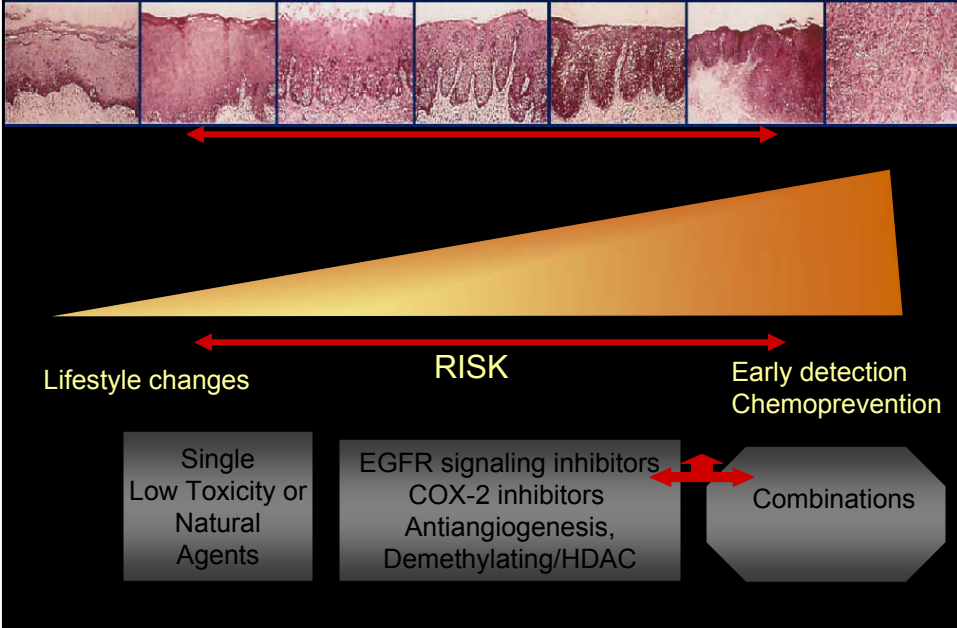


1 Grades of dysplasia has no bearing on outcome.

2 Total excision does not prevent carcinoma



# Targeted Chemoprevention



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JOURNAL OF CLINICAL ONCOLOGY

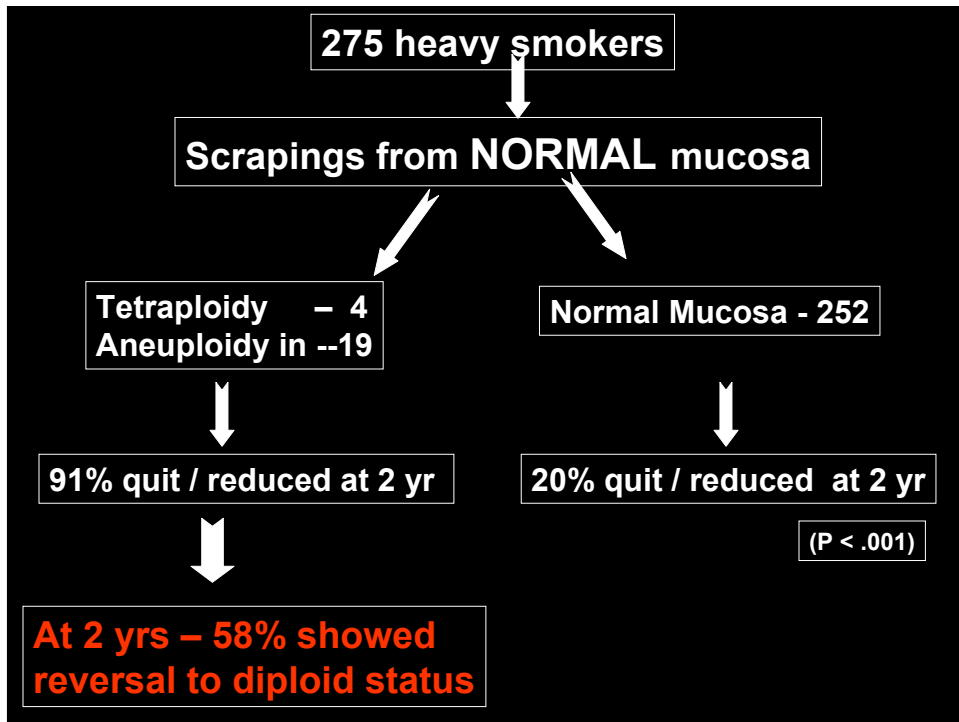
ORIGINAL REPORT

## Risk Markers of Oral Cancer in Clinically Normal Mucosa As an Aid in Smoking Cessation Counseling

*Jon Sudbe, Roy Samuelsson, Björn Risberg, Stig Heistein, Christian Nyhus, Margaretha Samuelsson, Ruth Pantervold, Eva Sigstad, Ben Davidson, Albrecht Reith, and Åsmund Berner*

From the Department of Medical Oncology and Radiotherapy, Division of

A B S T R A C T



## Conclusions

- Oral cancer- global health problem
- Primary & secondary prevention shows promise
- However, evidence not conclusive
- Tobacco counseling to be pursued
- Continued need for opportunistic screening of high risk individuals



**Thank you**



**THANK-YOU**