



SMOKEL ESS TOBACCO No less Harmful

Bibliography



ENVIS Centre



National Institute of Occupational Health
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SMOKELESS TOBACCO

No less harmful

(Bibliography)

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P R E F A C E

Smokeless tobacco are the cheapest, least taxed and most commonly used tobacco products in India. They are highly addictive and high in carcinogens. They cause a broad spectrum of diseases; yet awareness about their ill-effects is low. Smokeless tobacco products containing arecanut, e.g. gutka and mawa, are especially addictive and carcinogenic. Smokeless tobacco is used in almost one-third of households in rural areas whereas almost one-sixth of households in urban areas. Smokeless Tobacco may refer to Dipping tobacco (a type of tobacco that is placed between the lower or upper lip and gums), Chewing Tobacco (a type of tobacco that is chewed), Snuff (a type of tobacco that is inhaled or "snuffed" through the nose), Snus (a Swedish product similar to dipping tobacco), Creamy snuff (a fluid tobacco mixture marketed as a dental hygiene aid, albeit used for recreation)

All Smokeless tobacco contain nicotine, a potent addictive substance. Chewing allows nicotine, which is a drug you can become addicted to, to be absorbed into the bloodstream through the tissues in your mouth. They also contain carcinogenic tobacco-specific nitrosamines, albeit at differing levels. Smokeless tobacco is carcinogenic to humans and the pancreas has been identified as a main target organ. It can cause localized oral lesions, oral cancer and fatal myocardial infarction etc.

This bibliography is prepared on the basis of the available data on smokeless tobacco and health effect from India. The data were collected through searching various databases such as pub med, Medline, Toxline and other websites such as Google and consulting various journals and arranged chronologically. We are thankful to the Ministry of Environment and Forest (MoEF) for financial assistance and Dr. SP Sharma Project Director (EI), MoEF for constant encouragement and suggestions.

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1. Kausar, S. Giri, M. Mazumdar, A. Giri, P. Roy, P. Dhar

Micronucleus and other nuclear abnormalities among betel quid chewers with or without sadagura, a unique smokeless tobacco preparation, in a population from North East India
Mutat Res. 2009 May 22.

Department of Life Science, Assam University, Silchar-788011. Assam, India.

Genotoxicity is one of the important endpoints for risk assessment of various lifestyle factors. The study is the first report on the genotoxic effect associated with sadagura, a unique smokeless tobacco prepared in southern Assam province of North-East India. Sadagura is consumed with or without betel quid and/or smoking. In the present cytogenetic monitoring study, analysis of micronucleus (MN), nuclear bud, binucleated, karyorrhectic, karyolytic and pyknotic cells tests were performed in the exfoliated buccal cells of 75 habituates and compared to controls matched for gender, age, and habit. Significant increase in the frequency of MN was found in sadagura chewers (0.48%, $P < 0.001$), smokers (0.46%, $P < 0.01$), betel quid with sadagura chewers (0.91%, $P < 0.001$) and smokers chewing betel quid with sadagura (0.53%, $P < 0.001$) as compared to the unexposed control group (0.07%). Betel quid chewers showed significant increase (1.65%, $P < 0.05$) in the frequency of binucleated cells as compared to the control group (0.16%). Results of this study demonstrated that sadagura consumed as a single agent or in combination with betel quid, leads to a significant induction of cytogenetic damage in the buccal epithelial cells of habituates. We suggest that analysis of other degenerative nuclear changes in addition to MN can provide valuable information while evaluating potential genotoxic agents.

2. Das S, Neogy S, Gautam N, Roy S.

In vitro nicotine induced superoxide mediated DNA fragmentation in lymphocytes: protective role of Andrographis paniculata Nees.

Toxicol In Vitro. 2009; ;23(1): 90-8.

Immunology and Microbiology Laboratory, Department of Human Physiology with Community Health, Vidyasagar University, Midnapore 721 102, West Bengal, India.

Nicotine is a pharmacologically active substance and potent recreational drug present in smoke and smokeless tobacco products. The present study was initiated to investigate the protective role of Andrographis paniculata products (andrographolide and aqueous extract) on in vitro nicotine induced lymphocyte toxicity. Andrographolide and aqueous extract was isolated and characterized by HPLC, FTIR, TLC and biochemical assays. Significant ($P < 0.05$) increase of superoxide anion generation, lipid peroxidation, protein

oxidation and DNA fragmentation and decrease of cell viability, SOD and GSH content were observed in both 10mM and 100mM nicotine exposure. Different concentration of andrographolide and aqueous extract from *A. paniculata* supplement decreased oxidative stress in lymphocytes with the fall in superoxide anion generation, lipid peroxidation, protein oxidation, DNA fragmentation and rise in cell viability and the activities of the antioxidant enzymes; SOD and GSH. The above findings indicate that *A. paniculata* products modulate the nicotine-induced toxicity in lymphocytes through decreased superoxide mediated oxidative stress and DNA fragmentation. Hence, *A. paniculata* can be used as therapeutic means against nicotine mediated lymphocytes function.

3. Das S, Neogy S, Gautam N, Roy S.

Economic cost of tobacco use in India, 2004.

Tob Control. 2009 Apr; 18(2): 138-43.

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Objective: To estimate the tobacco-attributable costs of diseases separately for smoked and smokeless tobacco use in India.

Methods: The prevalence-based attributable-risk approach was used to estimate the economic cost of tobacco using healthcare expenditure data from the National Sample Survey, a nationally representative household sample survey conducted in India in 2004. Four major categories of tobacco-related disease-tuberculosis, respiratory diseases, cardiovascular diseases and neoplasms-were considered.

Results: Direct medical costs of treating tobacco related diseases in India amounted to \$907 million for smoked tobacco and \$285 million for smokeless tobacco. The indirect morbidity costs of tobacco use, which includes the cost of caregivers and value of work loss due to illness, amounted to \$398 million for smoked tobacco and \$104 million for smokeless tobacco. The total economic cost of tobacco use amounted to \$1.7 billion. Tuberculosis accounted for 18% of tobacco-related costs (\$311 million) in India. Of the total cost of tobacco, 88% was attributed to men.

Conclusions: The cost of tobacco use was many times more than the expenditures on tobacco control by the government of India and about 16% more than the total tax revenue from tobacco. The tobacco-attributable cost of tuberculosis was three times higher than the expenditure on tuberculosis control in India. The economic costs estimated here do not include the costs of premature mortality from tobacco use, which is known to comprise roughly 50-80% of the total economic cost of tobacco in many countries.

4. Misra C, Majumder M, Bajaj S, Ghosh S, Roy B, Roychoudhury S.

Polymorphisms at p53, p73, and MDM2 loci modulate the risk of tobacco associated leukoplakia and oral cancer.

Mol Carcinog. 2009; 9.

Molecular & Human Genetics Division, Indian Institute of Chemical Biology, Kolkata, India.

Polymorphisms at loci controlling cellular processes such as cell cycle, DNA repair, and apoptosis may modulate the risk of cancer. We examined the association of two linked polymorphisms (G4C14-A4T14) at p73 and one polymorphism (309G > T) at MDM2 promoter with the risk of leukoplakia and oral cancer. The p73 and MDM2 genotypes were determined in 197 leukoplakia patients, 310 oral cancer patients and in 348 healthy control subjects. The p73 GC/AT genotype increased the risk of leukoplakia (OR = 1.6, 95% CI = 1.1-2.3) and oral cancer (OR = 2.4, 95% CI = 1.7-3.3) but the 309G > T MDM2 polymorphism independently could not modify the risk of any of the diseases. Stratification of the study population into subgroups with different tobacco habits showed that the risk of the oral cancer is not modified further for the individuals carrying p73 risk genotype. However, leukoplakia patients with smokeless tobacco habit showed increased risk with combined GC/AT and AT/AT (OR = 3.0, 95% CI = 1.3-7.0) genotypes. A combined analysis was done with our previous published data on p53 codon 72 pro/arg polymorphism. Analysis of pair wise genotype combinations revealed increase in risk for specific p73-MDM2 and p73-p53 genotype combinations. Finally, the combined three loci analyses revealed that the presence of at least one risk allele at all three loci increases the risk of both leukoplakia and oral cancer.

5. P A Jayalekshmi, P Gangadharan, S Akiba, R R K Nair, M Tsuji, B Rajan

Tobacco chewing and female oral cavity cancer risk in Karunagappally cohort, India

British Journal of Cancer, 2009; 100, 848-852.

Dr PA Jayalekshmi, Natural Background Radiation Cancer Registry, Puthenthura.P.O, Neendakara, Kollam, Kerala 691588, India. www.bjcancer.com
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This study examined oral cancer in a cohort of 78 140 women aged 30–84 years in Karunagappally, Kerala, India, on whom baseline information was collected on lifestyle, including tobacco chewing, and sociodemographic factors during the period 1990–1997. By the end of 2005, 92 oral cancer cases were identified by the Karunagappally Cancer Registry. Poisson regression analysis of grouped data, taking into account age and income, showed that oral cancer incidence was strongly related to daily frequency of tobacco chewing ($P < 0.001$) and was increased 9.2-fold among women chewing tobacco 10 times or more a day. The

risk increased with the duration of tobacco chewing during the first 20 years of tobacco chewing. Age at starting tobacco chewing was not significantly related to oral cancer risk. This is the first cohort study of oral cancer in relation to tobacco chewing among women.

6. G. Harikiran, S. K. Pallavi, S. Hariprakash, K. S. Nagesh

Oral health-related KAP among 11- to 12-year-old school children in a government-aided missionary school of Bangalore city

Indian J Dent Res. 2008 Jul-Sep;19(3):236-42.

Department of Preventive and Community Dentistry, DAPMRV Dental College, Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka, India.

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Background: To organize community-oriented oral health promotion programs systematic analysis of the oral health situation would be needed, including information on oral health knowledge, attitudes, and practices (KAP).

Aim: The aim of this study was to assess knowledge, attitude, and practice (KAP) toward oral health among 11 to 12-year-old school children in a government-aided missionary school of Bangalore city.

Materials and Methods: The study group comprised of 212 children (Male: 108; Female; 104) who were in the age group of 11-12 years studying in a government-aided missionary school of Bangalore city. Data on oral health KAP were collected by means of a self-administered questionnaire. Statistical significance was determined by Chi-square test.

Results: This survey found that only 38.5% of the children brush their teeth two or more times a day. Pain and discomfort from teeth (35.1%) were common while dental visits were infrequent. Fear of the dentist was the main cause of irregular visit in 46.1% of study participants. High proportion of study participants reported having hidden sugar at least once a day: soft drinks (32.1%), milk with sugar (65.9%), and tea with sugar (56.1%). It was found that 5.4% and 3.9% of study participants smoke and chew tobacco, respectively.

Conclusion: Results of this study suggest that oral health KAP of study participants are poor and needs to be improved. Systematic community-oriented oral health promotion programs are needed to improve oral health KAP of school children.

7. Krishnan, B. Shah, V. Lal, D. K. Shukla, E. Paul, S. K. Kapoor

Prevalence of risk factors for non-communicable disease in a rural area of Faridabad district of Haryana

Indian J Public Health. 2008 Jul-Sep;52(3):117-24.

Background & Objectives: To estimate the prevalence and levels of common risk factors for noncommunicable disease in a rural population of Haryana.

Methods: The study involved a survey of 1359 male and 1469 female respondents, aged 15-64 years. Multistage sampling was used for recruitment (PHCs/sub-centres/villages). All households in the selected villages were covered, with one male and one female interviewed in alternate household. WHO STEP-wise tool was used as the study instrument which included behavioural risk factor questionnaire and physical measurements of height, weight, waist circumference and blood pressure. The age adjusting was done using rural Faridabad data from Census 2001.

Results: The age adjusted prevalence of daily smoked tobacco was 41% for men and 13% for women. Daily smokeless tobacco use was 7.1% and 1.2% for men and women respectively. The prevalence of current alcohol consumption was 24.6% among men and none of the women reported consuming alcohol. The mean number of servings of fruits and vegetables per day was 3.7 for men and 2.7 for women. The percentage of people undertaking at least 150 minutes of physical activity in a week was 77.8% for men and 54.5% for women. Among men 9.0% had BMI ≥ 25.0 compared to 15.2% among women. The prevalence of measured hypertension, i.e. ≥ 140 SBP and/or ≥ 90 DBP or on antihypertensive drugs was 10.7% among men and 7.9% among women.

Conclusion: The study showed a high burden of tobacco use and alcohol use among men, inactivity and overweight among women and low fruit and vegetable consumption among both sexes in rural areas.

8. Daniel AB, Nagaraj K, Kamath R.

Prevalence and determinants of tobacco use in a highly literate rural community in southern India.

Natl Med J India. 2008; 21(4): 163-5.

Department of Community Medicine, Kasturba Medical College, Manipal 576104, Karnataka, India. anjali.daniel@manipal.edu

Background: The adverse effects of tobacco use on the health of an individual are well known. It is essential to identify factors leading to tobacco use to plan strategies to limit its use. Education is known to influence the prevalence of tobacco use. We aimed to determine the prevalence and patterns of tobacco use in a rural community with a high literacy rate and to examine the socioeconomic and demographic correlates of tobacco consumption in the area.

Methods: A cross-sectional survey using personal interviews was carried out on 832 individuals >15 years of age. The prevalence of current daily use of tobacco was used

as the outcome measure. The main analytical methods used were chi-square test and multiple logistic regression analysis.

Results: The prevalence of tobacco use was 17.5%, being common among older persons, the lower socioeconomic group and those who were less educated. Tobacco was used predominantly in smokeless forms (chewing, snuff or both). The commonest reason cited for initiating tobacco use was to relieve toothache.

Conclusions: Our findings in this rural community suggest that improvement in the educational and socioeconomic status may lead to a decline in the use of tobacco. Health education to improve dental hygiene may also help to reduce tobacco use in this community as it is predominantly used in the chewing form.

9. Dar NA, Mir MM, Salam I, Malik MA, Gulzar GM, Yattoo GN, Ahmad A, Shah A.

Association between copper excess, zinc deficiency, and TP53 mutations in esophageal squamous cell carcinoma from Kashmir Valley, India-a high risk area.

Nutr Cancer,2008; 60(5): 585-91.

Department of Clinical Biochemistry, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India.

Trace element deficiency or excess is implicated in the development or progression in some cancers. Here we report the elevated level of copper and low level of zinc in the plasma of esophageal cancer patients in Kashmir India--a high incidence area. The average level of copper was significantly higher ($P < 0.0001$) for patients than for controls, with a mean concentration of $169 \mu\text{g/dl}$ and $149 \mu\text{g/dl}$ for patients and controls, respectively. The control group consisted of 55 healthy individuals matched for age, sex, and place of residence of the patients. In contrast, the average level of zinc in patients was significantly lower than in controls ($P < 0.0001$), with a mean concentration of $86.8 \mu\text{g/dl}$ and $96.1 \mu\text{g/dl}$ for patients and controls, respectively. The levels of both copper and zinc showed significant differences based on gender and age in patients as compared to controls. Similarly, smokers depicted a significant increase in serum copper ($N=39$, $P=0.002$) and a decrease in serum zinc approaching level of significance in the patient group as compared to controls. The copper and zinc levels were significantly altered in patients ($N=40$) when compared to controls as a function of snuff consumption. The differences in the levels of copper and zinc showed significant association with the consumption of local salted tea up to 1,500 ml per day, but the changes were insignificant beyond that. Patients with poorly differentiated tumors ($N=7$) had a higher copper concentration than those with moderately or well-differentiated tumors ($P < 0.0001$). To validate the general notion that imbalance in copper and zinc levels may lead to higher prevalence of TP53 mutations, we compared the 3 variables, and no association was found between copper concentration and TP53 mutation status; but

patients with TP53 mutant tumor had lower zinc levels than those with no mutation. In conclusion, our results point toward a role of the trace element imbalance in the esophageal tumorigenesis in high-risk Kashmiri population exposed to a range of nitroso compounds or their precursors. Further prospective cohort studies are warranted to determine whether change in the plasma zinc and copper homeostasis may represent an independent risk factor for this malignancy as well as a possible target for preventive intervention.

10. Gupta R, Sharma SC, Das SN.

Association of TNF-alpha and TNFR1 promoters and 3' UTR region of TNFR2 gene polymorphisms with genetic susceptibility to tobacco-related oral carcinoma in Asian Indians.

Oral Oncol. 2008 May;44(5):455-63.

Department of Biotechnology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

Tobacco-related oral squamous cell carcinoma is a common malignancy in Asian people. It accounts for almost 40% of cancers among Indian men and 3% in the Western world. Smokeless tobacco has been shown to induce tumor necrosis factor-alpha (TNF-alpha), which, along with its receptors, is over-expressed in people with oral carcinoma. Single nucleotide polymorphisms (SNPs) in TNF-alpha and TNF receptor genes may affect their expression and may be a potential determinant of susceptibility to tobacco-related oral carcinomas. We assessed SNPs in TNF-alpha(-308, -238) and TNF receptor 1 (TNFR1; -609) promoters by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and at four sites of TNF receptor 2 gene (TNFR2; exon 9 site 1176; exon 10 sites 1663, 1668 and 1690) by PCR-sequence-specific primers (PCR-SSP) techniques, respectively, in 94 patients and 130 healthy controls. TNF-alpha-308 G allele was significantly lower ($P_c=0.004$; $OR=3.85$), whereas A allele was significantly higher ($P_c=0.004$; $OR=0.25$) in patients compared with controls. No significant change was observed at -238 promoter site between the two groups. In the case of TNF receptors, both TNFR1 -609 TT ($P_c=0.006$; $OR=15.3$) and TNFR2 1690 CT ($P_c=0.018$; $OR=5.6$) genotypes were significantly lower in patients compared with controls. It seems that TNF-alpha-308 G/A may be related to susceptibility, whereas -609 TT TNFR1 and 1690 C/T TNFR2 SNPs may be protective to tobacco-related oral squamous cell carcinoma. These SNPs may be useful as a marker for high-risk groups among Asian Indians.

11. J. Kuruvilla

Utilizing dental colleges for the eradication of oral cancer in India

Indian J Dent Res. 2008 Oct-Dec;19(4):349-53.

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Dental education in India has grown in such a way that it ranks first in the world in having the highest number of dental schools. There are 240 dental schools all over the country. Paradoxically, even with this large number of dentists and dental institutions, India contributes to the highest number of incident cases of oral cancer. In India, oral cancer burden approximates to 20-30% of all cancers. The plausible reason for this high incidence of oral cancer could be expounded on the fact that there exists a high usage of tobacco within the country. The evidence for the high prevalence of using chewable tobacco products, especially in the youth, was recently reported in the Global Youth Tobacco Survey. This increasing usage of chewing tobacco and related products will further accrue to the mortality and morbidity figures in the near future. To effectuate a breakthrough in the existing situation, the work force of dental schools could be capitalized on. The aim of this article is to present the burden of oral cancer in the country and identify trends in the prevalence of tobacco usage, which if continues could alert an epidemic of oral cancer in the near future; and how dental schools in the country can be utilized for preventing this upcoming epidemic.

12. Pandey M, Prakash O, Santhi WS, Soumithran CS, Pillai RM.

Overexpression of COX-2 gene in oral cancer is independent of stage of disease and degree of differentiation.

Int J Oral Maxillofac Surg. 2008 Apr;37(4):379-83.

Department of Surgical Oncology, Regional Cancer Centre, Trivandrum, Kerala, India.

The incidence of oral cancer is high in certain parts of the world including Southeast Asia. Smokeless tobacco and areca nut chewing is proposed as a possible factor. Cyclooxygenase 2 (COX-2) receptors are present on neoplastic cells and are proposed to participate in initiation, transformation, progression and metastasis of cancer. In a prospective case-controlled study, 42 cases of squamous cell carcinoma of the oral cavity, 13 cases of oral premalignant lesions, and oral mucosa from 32 normal subjects were evaluated for COX-2 gene expression using reverse transcriptase polymerase chain reaction. The mean age of the patients with oral cancer was 60.2 years. The majority of cancer patients were males while the majority of controls were females. A significantly higher expression of COX-2 was found in cancer patients compared to both normal controls ($p=0.0001$) and patients with premalignant lesions (0.015). The expression in premalignant lesions was higher compared to healthy subjects ($p=0.05$). COX-2 expression in oral cancer was found to be independent of grade of tumor and

stage of disease. These results show up-regulation of the COX-2 gene in oral cancer and precancer. This suggests a role for COX2 receptors in oral cancer carcinogenesis, and provides the foundation for a large randomized trial to determine the role COX2 inhibitors may play in prevention of oral carcinogenesis.

13. Parmar G, Sangwan P, Vashi P, Kulkarni P, Kumar S.

Effect of chewing a mixture of areca nut and tobacco on periodontal tissues and oral hygiene status.

J Oral Sci. 2008 Mar;50(1):57-62

Department of Operative Dentistry, Government Dental College and Hospital, Civil Hospital Campus, Ahmedabad, India.

The present study was conducted to clarify the effects of chewing a quid containing areca nut and tobacco on periodontal tissue and oral hygiene status. A total of 365 subjects (168 chewers and 197 non-chewers with a mean age of 32.5 ± 0.7 and 30.4 ± 0.8 years, respectively) were enrolled. Clinical data on periodontal tissues, oral hygiene status, as well as information on bleeding from gums, ulcers in the oral cavity, or a burning sensation in the soft tissues, were collected as indicators of the possible presence and extent of periodontal lesions. The results indicated that a significantly higher number of quid-chewers suffered bleeding from the gums, halitosis, difficulty in opening the mouth and swallowing solid food, a burning sensation in the soft tissues, and ulcers in the oral cavity than non-chewers. There was no significant difference between quid-chewers and non-chewers with respect to oral hygiene measures adopted. However, clinical examination using the oral hygiene index score indicated that the oral hygiene status of quid-chewers was significantly deteriorated. The effect of quid-chewing on the periodontium, i.e. the occurrence of periodontal pockets, gingival lesions and gum recession, were significantly higher in quid-chewers than in non-chewers. Age, sex and smoking adjusted odds ratios for quid-chewers against non-chewers using logistic regression analysis indicated that, in general, chewers were at significantly higher risk for various oral complaints and periodontium status. The present data indicate that chewing quid comprising areca nut and tobacco has adverse effects on periodontal tissues, oral hygiene and incidence of oral lesions.

14. Pednekar MS, Gupta PC, Hebert JR, Hakama M.

Joint effects of tobacco use and body mass on all-cause mortality in Mumbai, India: results from a population-based cohort study.

Am J Epidemiol. 2008 Feb 1;167(3):330-40.

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The joint effects of tobacco use and body mass on mortality have not been well characterized, although evidence regarding the effect of smoking on the association between body mass and mortality is accumulating. To study the joint effects of these important risk factors, the authors conducted a prospective cohort study of 148,173 men and women aged ≥ 35 years in Mumbai, India. Subjects were recruited during 1991-1997 and then followed for approximately 5-6 years (1997-2003). During 774,129 person-years of follow-up, 13,261 deaths were observed. Tobacco use increased the risk of death across different categories of body mass, with particularly high risks being observed in extreme body mass categories. Among men, obese smokers and obese never users of tobacco were at 56% and 34% increased risks of death, respectively, compared with overweight never users of tobacco. Similarly, at highest risk were extremely thin males who smoked bidis (relative risk = 3.45) or cigarettes (relative risk = 3.32). Body mass and all forms of tobacco use had independent as well as multiplicative joint effects on mortality risk. Tobacco use and undernutrition are serious problems in India. The current study indicates that obesity may emerge as a serious public health problem with which tobacco use may interact.

15. R. Basu, S. Mandal, A. Ghosh, T. K. Poddar

Role of tobacco in the development of head and neck squamous cell carcinoma in an eastern Indian population

Asian Pac J Cancer Prev. 2008 Jul-Sep;9(3):381-6.

Vivekananda College, Thakurpukur, Kolkata, India.

The head and neck squamous cell carcinoma (HNSCC) accounts for about 30-40% of all cancer types in India and the subcontinent in general. HNSCCs are primarily not hereditary, but rather a disease of older and middle aged adults. Many etiological factors like tobacco, alcohol and HPV infection are known to play important roles. Eastern India, particularly Kolkata, has a population heavily exposed to various types of smoked and smokeless tobacco, with only limited exposure to alcoholic beverages. Since there have been no previous epidemiological studies on tobacco as the main risk factor for head and neck carcinogenesis in Kolkata, we here carried out a hospital based case control study in the city and its adjoin regions. Data from 110 patients diagnosed with HNSCC and a similar number of matched control samples were analyzed using the chi-square test. Survival status of the patients was also analyzed using the Kaplan-Meier method. A tobacco habit was significantly correlated with the incidence of HNSCC and persons with current addiction had a 2.17 fold increased risk of cancer development. Dose-response relationships were seen for the frequency ($p=0.01$) and duration ($p=0.02$) of tobacco exposure with the risk. No significant difference in impact was found with smoked as opposed to smokeless tobacco in the

development of the disease. Among HNSCC patients, significant poor survival in cases with tobacco habit than in those with no addiction and in cases with >10 years of addiction than in those with 10 years of addiction. Our data suggest that tobacco in both smoked and smokeless forms is the most important risk factor for both development and prognosis of HNSCCs and may be a major source of field cancerization on the head and neck epithelium in the eastern Indian population.

16. Sawant SS, Zingde SM, Vaidya MM.

Cytokeratin fragments in the serum: their utility for the management of oral cancer.

Oral Oncol. 2008 Aug;44(8):722-32.

Tata Memorial Centre, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Navi Mumbai 410 210, Maharashtra, India.

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy and is a major cause of cancer morbidity and mortality worldwide. Oral cancer is the most predominant malignancy in the Indian subcontinent due to the widespread habits of chewing tobacco and related products. Patients with oral tumours have a high risk of early locoregional relapse. Early detection of disease progression remains a challenging task mainly due to the lack of adequate early prognostic markers. CEA, SCC Ag, CA-125, serum cytokeratin (CK) fragments, Cyfra 21-1 (CK 19), TPS (CK 18), TPA (CK 8, 18, and 19) etc. are being used as serum markers for the prediction of prognosis of various malignancies. This review presents the available literature on serum CK markers in different malignancies evaluates their utility in the management of oral cancer, and identifies the lacunae which need to be addressed to develop sensitive and specific assays for early detection of recurrence, prognosis, and treatment monitoring.

17. Singh M, Shah PP, Singh AP, Ruwali M, Mathur N, Pant MC, Parmar D.

Association of genetic polymorphisms in glutathione S-transferases and susceptibility to head and neck cancer.

Mutat Res. 2008 Feb 1;638(1-2):184-94.

Developmental Toxicology Research Centre, P.O. Box 80, M.G. Marg, Lucknow 226001, India.

Polymorphism in glutathione S-transferase (GST) genes (GSTM1, GSTT1 and GSTP1) and interaction with environmental factors such as tobacco (smoking or chewing) and alcohol on susceptibility to head and neck squamous cell carcinoma (HNSCC) was studied in a case-control study. The study group consisted of 175 patients suffering from HNSCC and 200 age matched healthy controls. Statistical analysis showed an increase in risk to HNSCC in the patients with null genotype of GSTM1 (OR: 2.02; 95% CI: 1.32-3.10; P=0.001) or GSTT1 (OR: 1.66; 95% CI: 1.02-2.69; P=0.04), though the risk was

not found to be significant when adjusted for age, sex, smoking, tobacco chewing or alcohol use by multivariate logistic regression model. Our data further showed that combination of deletion genotypes of GST (GSTM1 and GSTT1) confer an even higher risk of HNSCC. Interestingly, GSTP1 wild type genotype in combination with GSTM1 null or GSTT1 null genotype increased susceptibility for HNSCC (OR: 2.49 and 2.75, respectively). Likewise a much greater risk for HNSCC was observed in the patients carrying a genotype combination of GSTM1 null, GSTT1 null and GSTP1 (Ile/Ile) (OR: 4.47; 95% CI: 1.62-12.31; P=0.002). Our data have further provided evidence that tobacco chewing and alcohol consumption are the important risk factors for HNSCC. The interaction between tobacco chewing and null genotype of GSTM1 or GSTT1 resulted in about 3.5- and 2.2-fold increase in the risk respectively in the patients when compared to those not chewing tobacco. Alcohol use resulted in more than 4-fold increase in the risk in the patients with null genotype of GSTM1 as compared to those who are non-drinkers. Alcohol consumption also increased the risk (approx. 3-fold) in the cases with null genotype of GSTT1, though the association was not found to be significant when compared to non-drinkers. Our data have provided evidence that GST polymorphism modifies the susceptibility to HNSCC and have further demonstrated importance of gene-environment interaction in modulating the risk to HNSCC.

18. Subramoney S, Gupta PC.

Anemia in pregnant women who use smokeless tobacco.

Nicotine Tob Res. 2008 May;10(5):917-20

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A significantly higher mean hemoglobin level in women smokers in comparison to nonsmokers with a generalized rightward shift of the hemoglobin distribution curve has been reported at the population level. Studies on pregnant women, however, have often associated smoking with decreased hemoglobin levels, although not consistently. We examined whether smokeless tobacco use during pregnancy influenced hemoglobin levels in a population-based cohort of 918 pregnant women in Mumbai, India. Mean hemoglobin levels (Hb) were significantly lower in users (10.00 g/dl) compared with nonusers (10.46 g/dl), $p < .000$. Anemia (Hb < 10 g/dl) was significantly associated with smokeless tobacco in the univariate analysis (OR = 1.7, 95% CI 1.2-2.5). There was no change after adjusting odds ratios for potential confounders in multivariate analysis (OR=1.7, 95% CI 1.2-2.5). The odds ratios for anemia were adjusted for age of mother, education, socioeconomic status, type of residence, lower body mass index, parity, vegetarian or nonvegetarian food habit, and hemodilution during pregnancy. The results suggest that smokeless tobacco use during pregnancy is associated with lower hemoglobin levels, as has often been observed with cigarette smoking. Smokeless

tobacco use is widely prevalent among women in Southeast Asia and is gaining popularity across the world as a safe alternative to smoking. Further exploration and clarification of this association is therefore of considerable importance to public health.

19. Sumanth S, Bhat KM, Bhat GS.

Periodontal health status in pan chewers with or without the use of tobacco.

Oral Health Prev Dent. 2008;6(3):223-9.

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Background: Betel nut and tobacco chewing is a common practice in south-east Asia. In India, betel nut is commonly chewed in the form of pan, with or without tobacco. Numerous studies have shown the carcinogenic potential of betel nut and tobacco. Betel nut and tobacco are also known to have deleterious effects on the oral tissues.

Purpose: The aim of our study was to evaluate and compare the periodontal effects of pan chewing with or without the use of tobacco as an ingredient.

Materials & methods: The periodontal status of 300 subjects (150 subjects were pan chewers with tobacco and 150 subjects were pan chewers without tobacco) was evaluated using the community periodontal index (CPI). The subjects were selected by the stratified random sampling method. The oral hygiene status of the subjects was evaluated using the simplified oral hygiene index.

Results: CPI code-4, with a probing depth of 6 mm or more, was seen in 30% of pan chewers with tobacco compared with 7.3% of pan chewers without tobacco. It was found that pan chewers with tobacco had 4.7 times more risk of having pockets than pan chewers without tobacco. The higher codes of loss of attachment were seen in pan chewers with tobacco compared with pan chewers without tobacco. It was found that pan chewers with tobacco had 7 times more risk of having loss of attachment when compared with the pan chewers without tobacco.

Conclusions: The results show higher incidence of periodontal diseases in pan chewers who use tobacco compared with pan chewers who do not use tobacco. Based on the results, it was concluded that, although betel nut has deleterious effects on the periodontium, the addition of tobacco leads to a synergistic effect between betel nut and tobacco on the periodontal tissues.

20. V. K. Laxman, S. Annaji

Tobacco use and its effects on the periodontium and periodontal therapy

J Contemp Dent Pract. 2008 Nov 1;9(7):97-107.

Aim: The purpose of this article is to present a review of the potential biological mechanisms underlying the effects of tobacco smoking on periodontal health and periodontal therapy.

Background: Periodontitis is the result of complex interrelationships between infectious agents and host factors. Environmental, acquired, and genetic risk factors modify the expression of disease and may, therefore, affect the onset or progression of periodontitis.

Review results: The study of the relationship between periodontal disease and smoking has received increased attention during the last few years. Tobacco smoking has wide spread systemic effects, many of which may provide mechanisms for the increased susceptibility to periodontitis and the poorer response to treatment.

Conclusions: Tobacco smoking is a significant risk factor for periodontal disease.

Clinical significance: The role smoking plays in periodontal disease should be considered by clinicians and patients during active periodontal therapy and the oral health maintenance phases of care.

21. Yadav SS, Ruwali M, Shah PP, Mathur N, Singh RL, Pant MC, Parmar D.

Association of poor metabolizers of cytochrome P450 2C19 with head and neck cancer and poor treatment response.

Mutat Res. 2008 Sep 26;644(1-2):31-7.

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A case-control study consisting of 300 patients and an equal number of healthy controls was carried out to investigate the association of polymorphism in cytochrome P450 2C19 (CYP2C19), which results in poor and extensive metabolizers (PMs and EMs) genotypes, with squamous cell carcinoma of head and neck (HNSCC) and treatment response in patients receiving combination of chemo-radiotherapy. A higher frequency of CYP2C19 2 variants was observed in the cases resulting in significantly higher risk to HNSCC (Ad OR 3.36, 95% CI 1.94-5.82, p-value<0.05). The PM genotype of CYP2C19 3 was also found to be slightly increased in the cases, though the increase in risk was not significant when analyzed by multivariate logistic regression model. Tobacco chewing amongst the cases resulted in almost 13-fold increase in the risk with CYP2C19 2 (OR: 12.39) and 3-fold with CYP2C19 3 genotype (OR: 2.90) when compared to the tobacco chewers amongst the controls. Likewise, cigarette smoking in the cases increased the risk approximately 9-fold and 3-fold with CYP2C19 2 (OR: 8.93) and CYP2C19 3 (OR: 2.18) genotypes respectively when compared to smokers amongst the controls. Similar increase in risk was associated with alcohol use amongst the cases

carrying variant genotypes of CYP2C19 2 (OR: 7.75) or CYP2C19 3 (OR: 2.60), demonstrating the importance of gene-environment interaction in modifying susceptibility to HNSCC. Interestingly, patients with PMs of CYP2C19 (CYP2C19 2 and CYP2C19 3) exhibited little response to the respective chemotherapy than the patients carrying wild-type genotype demonstrating that functional enzyme deficiencies due to polymorphism in CYPs may not only be important in modifying the susceptibility to HNSCC but also in determining chemotherapeutic response.

22. Gangane N, Chawla S, Anshu, Gupta SS, Sharma SM.

Reassessment of risk factors for oral cancer.

Asian Pac J Cancer Prev. 2007 Apr-Jun;8(2):243-8.

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A total of 140 cases of histologically confirmed oral cancer were evaluated for their demographic details, dietary habits and addiction to tobacco and alcohol using a pre-designed structured questionnaire at the Mahatma Gandhi Institute of Medical Sciences, Sevagram in Central India. These cases were matched with three sets of age and sex matched controls. Oral cancer was predominant in the age group of 50-59 years. Individuals on a non-vegetarian diet appeared to be at greater risk of developing oral cancer. Cases were habituated to consuming hot beverages more frequently and milk less frequently than controls. Consumption of ghutka, a granular form of chewable tobacco and areca nut, was significantly associated with oral cancer cases. Cases had been using oral tobacco for longer duration than controls, and were habituated to sleeping with tobacco quid in their mouth. Most cases were also addicted to smoking tobacco and alcohol consumption. Bidi (a crude cigarette) smoking was most commonly associated with oral cancer. On stratified analysis, a combination of regular smoking and oral tobacco use, as well as a combination of regular alcohol intake and oral tobacco use were significantly associated with oral cancer cases. Synergistic effects of all three or even two of the risk factors - oral tobacco use, smoking and alcohol consumption- was more commonly seen in cases when compared to controls.

23. Gupta BK, Kaushik A, Panwar RB, Chaddha VS, Nayak KC, Singh VB, Gupta R, Raja S.

Cardiovascular risk factors in tobacco-chewers: a controlled study.

J Assoc Physicians India. 2007 Jan;55:27-31.

Departments of Medicine and Cardiology, SP Medical College and Associated Group of Hospitals, Bikaner-334001 Rajasthan.

Background: Influence of habitual tobacco chewing on cardiovascular risk has not been well studied. To determine prevalence of major cardiovascular risk factors in subjects who habitually chew tobacco we performed a controlled study.

Methods: A population based case-control study was performed in Bikaner in North-western India where the prevalence of tobacco-chewing is high. Successive 200 subjects who agreed to participate in the evaluation and had a history of isolated tobacco-chewing (range 10-60 years) were enrolled (Group III). The prevalence of major coronary risk factors- obesity, truncal obesity, hypertension, fasting hyperglycemia, and lipid levels were estimated using current guidelines. Electrocardiogram was also performed in all subjects. Chest radiography and treadmill stress test was done in subjects when indicated by symptoms. 200 age- and gender-matched controls who did not use tobacco in any form (Group I) and 200 subjects who had history of smoking bidis or cigarettes for more than 10 years (range 10-55 years) (Group II) were also evaluated.

Results: The body-mass index and obesity were lowest in smoker group. Tobacco chewers had a significantly higher ($p<0.001$) systolic blood pressure (BP), diastolic BP, resting heart rate, total cholesterol, LDL cholesterol and triglycerides as compared to controls and was similar to smoker group. There was a significantly greater ($p<0.01$) prevalence of hypertension, hypercholesterolemia, hypertriglyceridemia, radiographic cardiomegaly and positive stress test in Group III as compared to controls. Prevalence of these risk factors was similar among Group II and Group III subjects. HDL cholesterol levels were the lowest in tobacco-chewing group (44.3 ± 8.1 mg/dl) as compared to the Group I (48.4 ± 7.8) and Group II (47.4 ± 7.5) ($p<0.001$).

Conclusions: There is a significantly greater prevalence of multiple cardiovascular risk factors obesity, resting tachycardia, hypertension, high total and LDL cholesterol, and low HDL cholesterol, and electrocardiographic changes in tobacco users, chewing or smoking, as compared-to tobacco non-users. Chewing tobacco is associated with similar cardiovascular risk as smoking.

24. Hazarey VK, Erlewad DM, Mundhe KA, Ughade SN.

Oral submucous fibrosis: study of 1000 cases from central India.
J Oral Pathol Med. 2007 Jan;36(1):12-7.

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Background: Very few reports have been published on the gender specificity of oral submucous fibrosis (OSF) in relation to habit patterns and the severity of disease in the world literature. The purpose of the study was to ascertain the gender specificity for different habits and severity of OSF.

Methods: A hospital-based cross-sectional study on various habit patterns associated with OSF was performed in Nagpur over a 5-year period. A total of 1000 OSF cases from 266,418 out patients comprised the study sample.

Results: The male-to-female ratio of OSF was 4.9:1. Occurrence of OSF was at a significant younger age group (<30 years) among men when compared with women (OR=4.62, 3.22-6.63, P=0.0001). Reduced mouth opening, altered salivation and altered taste sensation were found to be significantly more prevalent in women when compared with men. Exclusive areca nut chewing habit was significantly more prevalent in women (OR= 44.5, 25.4-79.8, P=0.0001). Whereas significant increase for Gutkha (Areca quid with tobacco) (OR = 2.33, 1.56-3.54, P=0.0001) and kharra/Mawa (crude combination of areca nut and tobacco) (OR=6.8, 4.36-11.06, P=0.0001) chewing was found in men when compared with women.

Conclusions: There is a marked difference in literacy, socioeconomic status, areca nut chewing habits, symptoms and disease severity in women when compared with men in the central Indian population.

25. Jain M, Kumar S, Lal P, Tiwari A, Ghoshal UC, Mittal B.

Role of BCL2 (ala43thr), CCND1 (G870A) and FAS (A-670G) polymorphisms in modulating the risk of developing esophageal cancer.

Cancer Detect Prev. 2007;31(3):225-32.

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Background: Perturbations in the cell cycle and apoptotic genes have been implicated in human malignancies. A study of BCL2 ala43thr, CCND1 G870A and FAS A-670G gene polymorphisms was undertaken to explore their role in influencing the susceptibility for development of esophageal cancer.

Methods: A total of 151 patients and age and gender matched 201 controls were investigated for BCL2 ala43thr, CCND1 G870A and FAS A-670G polymorphisms by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP).

Results: The ala43ala genotype of BCL2 anti-apoptotic gene was significantly associated with risk of developing esophageal cancer (OR 2.1, 95%CI=1.0-4.4, P=0.03), more so in males (OR 2.6, 95%CI=P=0.03). In CCND1 G870A polymorphism, the AA genotype was marginally associated with higher risk of esophageal cancer (OR 1.5, 95%CI=0.98-2.4, P=0.05). No significant differences in genotype frequencies of FAS A-670G polymorphism were seen between esophageal cancer patients and controls (P=0.32). Interaction of BCL2 ala43ala, CCND1 870AA and FAS -670AA genotypes did not increase the risk multiplicatively. Association with clinical characteristics showed BCL2 ala43ala genotype to be at increased risk for developing tumors in the middle third

location (OR 2.3, 95%CI=1.0-5.3, P=0.03), while patients with CCND1 870AA genotypes were at higher risk for the development of cancer in the upper third location (OR 3.8, 95%CI=1.6-9, P=0.002). BCL2 ala43ala genotype did not modulate the cancer risk in tobacco users. However, patients with CCND1 870AA and FAS -670AA genotypes were associated with a significantly lower number of smoking and chewing pack-years, suggesting a dose-dependent interaction in the risk for esophageal cancer (P=0.005).

Conclusions: There appears to be an influence of BCL2 ala43ala and CCND1 870AA genotypes on esophageal cancer phenotype, particularly with regard to tumor location, which supports the theory of prevalence of site-specific genetic alterations. FAS A-670G was not associated with the risk of developing esophageal cancer. Gene-environment interaction analysis showed cancer susceptibility in CCND1 870AA and FAS -670AA genotype to be influenced by quantity of tobacco.

26. Majumder M, Sikdar N, Ghosh S, Roy B.

Polymorphisms at XPD and XRCC1 DNA repair loci and increased risk of oral leukoplakia and cancer among NAT2 slow acetylators.

Int J Cancer. 2007 May 15;120(10):2148-56

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Polymorphisms at N-acetyl transferase 2 locus (NAT2) lead to slow, intermediate and rapid acetylation properties of the enzyme. Improper acetylation of heterocyclic and aromatic amines, present in tobacco, might cause DNA adduct formation. Generally, DNA repair enzymes remove these adduct to escape malignancy. But, tobacco users carrying susceptible NAT2 and DNA repair loci might be at risk of oral leukoplakia and cancer. In this study, 389 controls, 224 leukoplakia and 310 cancer patients were genotyped at 5 polymorphic sites on NAT2 and 3 polymorphic sites on each of XRCC1 and XPD loci by PCR-RFLP method to determine the risk of the diseases. None of the SNPs on these loci independently could modify the risk of the diseases in overall population but variant genotype (Gln/Gln) at codon 399 on XRCC1 and major genotype (Lys/Lys) at codon 751 on XPD were associated with increased risk of leukoplakia and cancer among slow acetylators, respectively (OR=4.2, 95% CI=1.2-15.0; OR=1.6, 95% CI=1.1-2.3, respectively). Variant genotype (Asn/Asn) at codon 312 on XPD was also associated with increased risk of cancer among rapid and intermediate acetylators (OR=1.9, 95% CI=1.2-2.9). Variant C-G-A haplotype at XRCC1 was associated with increased risk of leukoplakia (OR=1.7, 95% CI = 1.2-2.4) but leukoplakia and cancer in mixed tobacco users (OR=3.1, 95% CI=1.4-7.1, OR=2.4, 95% CI=1.1-5.4, respectively) among slow acetylators. Although none of the 3 loci could modulate the risk of the

diseases independently but 2 loci in combination, working in 2 different biochemical pathways, could do so in these patient populations.

27. Nagpal JK, Das BR

Identification of differentially expressed genes in tobacco chewing-mediated oral cancer by differential display-polymerase chain reaction.

Eur J Clin Invest. 2007 Aug;37(8):658-64.

Institute of Life Sciences, Bhubaneswar, India.

Background: Identification of changes in gene expression that occur in oral squamous cell carcinoma (OSCC), after sufficient characterization, may yield novel molecular markers that may be useful in the diagnosis and disease management of oral cancer.

Materials and methods: We used differential display-polymerase chain reaction (DD-PCR) to study critically the global gene expression profile of the oral tumour versus normal epithelium. The differential expression of fished out cDNA were confirmed by Northern blot and reverse transcription-PCR. The differentially expressed cDNA were cloned, sequenced and matched for homology in the GenBank database.

Results: We identified 13 cDNA that showed differential expression. Out of these we selected four cDNA showing consistent reproducibility. One of the cDNA expressed exclusively in tumour had a homology to DEK, a putative oncogene, and is linked to leukaemia, various cancers, HIV infection and several autoimmune disorders. Another cDNA expressed only in tumour had homology to sorcin protein. Sorcin is a 22-kDa calcium-binding protein and is associated with drug resistance in various cell lines. Apparently, sorcin expression might be responsible for drug resistance of OSCC and poor prognosis. Another cDNA showing 10 times overexpression in cheek tumour as compared to normal had homology to CDK6 gene. Hence, it seems from our results that CDK6 is dysregulated during oral carcinogenesis. The fourth cDNA was overexpressed in normal as compared to cheek tumour, but did not show any match in BLAST search.

Conclusions: We conclude that there is an enormous significance of these differentially expressed cDNA in oral cancer progression as they can serve as cancer markers to be used for diagnosis and therapeutic intervention.

28. Pal D, Banerjee S, Indra D, Mandal S, Dum A, Bhowmik A, Panda CK, Das S.

Influence of regular black tea consumption on tobacco associated DNA damage and HPV prevalence in human oral mucosa.

Asian Pac J Cancer Prev. 2007 Apr-Jun;8(2):263-6.

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Black tea is more widely consumed than green tea worldwide, particularly in India. Therefore, it is necessary to focus attention on black tea with respect to its health promoting and anti-cancer actions. In order to establish the concept that black tea is a potential candidate for cancer prevention, it is important to provide epidemiological evidence derived from investigations of human populations. In view of this, the objective of the present study was to determine the correlation between nature of black tea consumption and DNA damage in normal subjects with or without tobacco habit and oral cancer patients, taking the latter as positive controls. Much experimental evidence points to associations between tobacco habit and HPV 16 and HPV 18 (Human Papilloma virus) infection. But no studies have taken into account the possible confounding effect of black tea consumption on DNA damage along with HPV infection. A pilot study was therefore undertaken. Comet assay was used to evaluate the DNA damage among normal subjects including tobacco users (n=86), non-tobacco users (n=45) and Oral cancer patients (n = 37). Percentage of damaged cells was scored in the buccal squamous cells of all subjects mentioned above. HPV analysis was performed on 79 samples (including 37 oral cancer patients). The evaluation of various confounding factors like age, tenure of tobacco habit and tea habit showed significant associations with DNA damage. The observations strongly indicate that regular intake of black tea at least above four cups can reduce tobacco associated DNA damage among normal tobacco users. HPV prevalence was not seen to be associated with age, tenure of tobacco habit or the tea drinking habit.

29. Patel BP, Rawal UM, Dave TK, Rawal RM, Shukla SN, Shah PM, Patel PS.

Lipid peroxidation, total antioxidant status, and total thiol levels predict overall survival in patients with oral squamous cell carcinoma.

Integr Cancer Ther. 2007 Dec;6(4):365-72

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Tobacco is the major etiological factor for oral cancer development through the generation of oxidative stress. Therefore, markers of oxidative stress such as total antioxidant status, lipid peroxidation, and total thiol levels might be useful to monitor oxidative stress and predict overall survival in oral cancer patients. The study included 140 oral cancer patients and 50 healthy controls, who were classified as with the habit of tobacco and no habit of tobacco. Adjacent normal and malignant tissue samples were collected from oral cancer patients. Plasma and tissue levels of lipid peroxidation, thiol, and total antioxidant status were assayed by spectrophotometric methods. Thiol levels were significantly lower in controls with the habit of tobacco ($P=0.033$), oral cancer patients ($P=0.0001$), and malignant tissues ($P=0.015$) as compared to controls with no

habit of tobacco, controls with the habit of tobacco, and adjacent normal tissues, respectively. Tobacco exposure was higher in oral cancer patients than controls with the habit of tobacco. Controls with the habit of tobacco who had lower thiol (odds ratio [OR]=10.58, P=0.008) and high tobacco exposure (OR=0.251, P=0.05) showed an elevated risk of oral cancer development. Patients showing a lipid peroxidation level above the cutoff level as compared to patients below the cutoff level showed poor overall survival, whereas those with thiol and total antioxidant status levels below the cutoff level as compared to their respective counterparts showed poor overall survival. In conclusion, lipid peroxidation and thiol could be useful for predicting the risk of oral carcinogenesis in healthy tobacco consumers and predicting overall survival of oral cancer patients.

30. Rajan G, Ramesh S, Sankaralingam S

Areca nut use in rural Tamil Nadu: a growing threat.

Indian J Med Sci. 2007 Jun;61(6):332-7

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Background: Areca nut is the fourth main psychoactive substance in the world. In India, tobacco is added to the quid and the commercially manufactured nonperishable forms of betel quid (pan masala or gutkha) are on the rise in the market.

Objective: To find out the prevalence of areca nut among the rural residents of Sriperambudur Taluk.

Setting and design: A community-based survey using pre-tested semi-structured questionnaire.

Materials and methods: The survey was conducted in 2 villages and their colonies, which were randomly selected out of 168 villages. Data was collected from 500 residents of the study population. The survey was conducted for a period of 2 months. Statistical Analysis: SPSS version 10.0.

Results: The study participants were more likely to initiate areca nut use by 22 years of age. As many as 19.8% (n = 99) of the study participants chewed areca nut products, out of whom 11.2% (n = 56) indulged in chewing habit alone (areca nut products). Areca nut use was higher among male study subjects compared to females. The commercial forms of areca nut products (gutkha) were the most prevalent ones [47.5% (n = 47) of those who used areca nut] observed in the community. Compared to female participants, male participants were more likely to perceive areca nut use as the most harmful habit draining the community health and wealth.

Conclusion: There seems to be an increase in the prevalence of areca nut use. The community also perceives it to be a harmful habit. Therefore, effective interventions

should be targeted towards the high-risk subpopulation of the community to decrease the prevalence of areca nut use in rural Tamil Nadu.

31. Sawhney M, Rohatgi N, Kaur J, Gupta SD, Deo SV, Shukla NK, Ralhan R.
MGMT expression in oral precancerous and cancerous lesions: correlation with progression, nodal metastasis and poor prognosis.

Oral Oncol. 2007 May;43(5):515-22.

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Alkylation of DNA at the O(6) position of guanine is a critical step in the induction of mutations by carcinogenic and chemotherapeutic alkylating agents. O(6)-methylguanine-DNA methyltransferase (MGMT) is an enzyme that removes mutagenic adducts from the O(6) position of guanine, thereby protecting the genome against guanine to adenine transitions. We hypothesized that alteration in MGMT expression might occur in early stages of development of oral cancer and be associated with disease progression. Immunohistochemical analysis of MGMT expression was carried out in 107 oral squamous cell carcinomas (OSCCs), 78 oral precancerous lesions (OPLs) (58 hyperplasias and 20 dysplasias) and 30 histologically normal oral tissues and correlated with clinicopathological parameters as well as major risk factors. Decreased MGMT expression was observed as early as in hyperplasia ($p=0.003$; Odd's Ratio (OR)=5.0). Significant loss of MGMT expression was observed from hyperplasia to dysplasia ($p=0.034$; OR=4.0). Loss of MGMT expression was associated with late clinical stage of OSCCs ($p=0.027$, OR=2.0) and nodal metastasis ($p=0.031$, OR=2.5). Decreased MGMT expression was associated with smokeless tobacco (ST) consumption in patients with OPLs ($p=0.017$, OR=3.6) and OSCCs ($p=0.031$, OR=2.8). Significant association was also observed between loss of MGMT expression and poor prognosis of OSCC patients ($p=0.02$; OR=5.2). The decreased MGMT expression in OPLs suggested that deregulation of MGMT expression is an early event in the development of oral cancer. In OSCCs, its correlation with late clinical stage, and nodal metastasis suggests association with aggressive tumor behavior and cancer progression, underscoring its potential as a candidate predictive marker for nodal metastasis and disease prognosis. Correlation of loss of MGMT expression with ST consumption underscored its significance in ST-associated oral carcinogenesis.

32. Sawhney M, Rohatgi N, Kaur J, Shishodia S, Sethi G, Gupta SD, Deo SV, Shukla NK, Aggarwal BB, Ralhan R.
Expression of NF-kappaB parallels COX-2 expression in oral precancer and cancer: association with smokeless tobacco.

Int J Cancer. 2007 Jun 15;120(12):2545-56

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Nuclear Factor-kappaB (NF-kappaB) activation and COX-2 overexpression have been reported in head and neck cancer, but the relationship between these proteins remains to be investigated. To determine the relationship between NF-kappaB and COX-2 in Smokeless Tobacco (ST) associated oral tumorigenesis, we performed immunohistochemistry in serial sections from 107 OSCCs, 78 oral precancerous lesions (OPLs) (58 hyperplasias, 20 dysplasias) and 15 histologically normal oral tissues and correlated with clinicopathological data. Significant increase in NF-kappaB and COX-2 immunopositivity was observed from normal oral mucosa to OPLs to OSCCs ($p=0.009$ and $p=0.002$ respectively). Upregulation of NF-kappaB and COX-2 was observed as early as in hyperplasia [$p=0.006$; OR=6.1 and $p=0.003$; OR=7.6, respectively]. Expression of both proteins was found to be significantly associated in OPLs ($p=0.000$; OR=12.6) and OSCCs ($p=0.001$; OR=4.0). Intriguingly, khaini consumption correlated with NF-kappaB immunopositivity in OPLs ($p=0.05$, OR=3.8) and OSCCs ($p=0.01$, OR=3.4) and with COX-2 expression in OPLs ($p=0.03$; OR=4.3). In vitro experimental system of ST associated oral carcinogenesis was used to demonstrate ST (khaini) and NNK mediated activation of NF-kappaB and COX-2, supporting the clinical data. In conclusion, this study demonstrates correlation between over expression of NF-kappaB and COX-2 in early precancerous stages of development of oral cancer and sustained elevation down the tumorigenic pathway, underscoring their potential as targets for early intervention. In vitro studies demonstrated that NNK may be one of the carcinogenic components of ST (khaini) inducing activation of NF-kappaB and COX-2 in oral precancer and cancer cells, suggesting plausible role in ST-induced oral carcinogenesis.

33. Singh RB, Singh S, Chattopadhyaya P, Singh K, Singhz V, Kulshrestha SK, Tomar RS, Kumar R, Singh G, Mechirova V, Pella D.

Tobacco consumption in relation to causes of death in an urban population of north India.

Int J Chron Obstruct Pulmon Dis. 2007;2(2):177-85.

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Background: Noncommunicable diseases have become a public health problem in India concomitant with economic development, leading to increases in tobacco consumption, obesity, and changes in diet and lifestyle. Although observation suggests that tobacco consumption is a major risk factor for deaths due to circulatory, pulmonary, and malignant diseases, such studies are not available from most populations in developing countries.

Subject and materials: For the period 1999-2001, we studied the randomly selected records of death of 2222 (1385 men and 837 women) decedents, aged 25-64 years, out of 3034 death records overall from the records at Municipal Corporation, Moradabad. All the families of these deceased could be contacted individually to find out the causes of death, by scientist/doctor administered, informed consented, verbal autopsy questionnaire, completed with the help of the spouse and local treating doctor practicing in the appropriate healthcare region. Social classes and tobacco intakes were assessed by a questionnaire.

Results: The prevalence of tobacco consumption, including chewing + smoking, were 45% (n = 623) among men and 15% (n = 125) among women decedents. However, smoking was observed in 20% and tobacco chewing in 30% of male decedents, while only 6% of female decedents smoked and 10% chewed tobacco. Social class had no impact on tobacco consumption in men but did influence one subgroup >55 years among women, ie, among those who had the highest tobacco consumption. Tobacco intakes were significantly more common among decedents dying due to circulatory, malignant, and pulmonary diseases, compared with other causes (men 61.1%, 76.6%, pulmonary 77.3% vs 31%, $P < 0.001$; women 27.5%, 75.9%, pulmonary 24.6% vs 0.42%, $P < 0.001$) of mortality, respectively. Pulmonary causes included chronic bronchitis and asthma. Circulatory diseases (29.1%, n=646) including heart attacks (10.0%), stroke (7.8%), valvular heart disease (7.2%, n=160), sudden cardiac death and inflammatory cardiac disease, each (2.0%, n=44) were the second most common causes of deaths, after infections (41.1%, n=915). Malignant neoplasm (5.8%, n=131), injury (14.0%, n=313), and miscellaneous causes of deaths, including diabetes mellitus (2.2%, n=49) were noted in 9.1%, (n=202) of death records. Cancers of the lung (1.6%), oral cavity (1.5%), liver (1.1%), stomach (0.9%), breast (0.31%), uterus, cervix, and ovary (0.27%) were relatively common causes for deaths due to malignancy.

Conclusion: This study shows that tobacco consumption appears to be a major contributor to deaths due to circulatory diseases and malignant diseases in India. Social class status had little impact on tobacco consumption in male decedents. Rapid changes in diet and lifestyle, increases in tobacco consumption, and possibly aging of the population, appear to be strongly associated with mortality due to cardiovascular diseases and cancer in this middle-income country.

34. Soya SS, Vinod T, Reddy KS, Gopalakrishnan S, Adithan C.

Genetic polymorphisms of glutathione-S-transferase genes (GSTM1, GSTT1 and GSTP1) and upper aerodigestive tract cancer risk among smokers, tobacco chewers and alcoholics in an Indian population.

Eur J Cancer. 2007 Dec;43(18):2698-706.

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The glutathione-S-transferase (GST) genes are involved in the detoxification of various carcinogens that increase the risk to upper aerodigestive tract (UADT) cancers. In the present study, 408 unrelated histopathologically confirmed cases and 220 population based controls, matched by age and gender, which belonged to the Tamilian population of south India were genotyped for polymorphisms in GSTM1, GSTT1 and GSTP1 using polymerase chain reaction (PCR) based methods. The multivariate logistic regression analyses demonstrated that GSTT1 null genotype was significantly associated with increased risk for UADT cancers (odds ratio (OR) 2.5; 95% confidence intervals (CIs) 1.3-4.7). The combined effects of GST genes have shown that concurrent lack of GSTM1 and GSTT1 had a significantly increased risk (OR 4.6; 95% CI 1.3-15.6), while GSTT1 null genotype along with GSTP1 polymorphic variants further increased the cancer risk (OR 5.3; 95% CI 2.0-13.6). The most remarkable risk was seen among individuals carrying GSTM1 null, GSTT1 null genotypes and GSTP1 polymorphic variants (OR 7.8; 95% CI 1.0-61.0). Tobacco chewers carrying GSTM1 null genotype had an enhanced risk for UADT cancers. An enhanced risk among tobacco chewers and alcoholics (regular) was noted in individuals with GSTT1 null genotype. Similarly, a significant interaction was observed among smokers (>40 pack-year (PY)) and tobacco chewers carrying GSTP1 mutant genotypes. Although the null genotype of GSTT1 is a strong predisposing risk factor for UADT cancers, we conclude that the significant gene-gene and gene-environment interactions of GST genes may confer a substantial risk to UADT cancers in the Tamilian population of south India.

35. Sreedharan S, Hegde MC, Pai R, Rhodrigues S, Kumar R, Rasheed A.

Snuff-induced malignancy of the nasal vestibule: a case report.
Am J Otolaryngol. 2007 Sep-Oct;28(5):353-6.

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The association between nasal snuff and malignancy is not well established. There is epidemiological evidence suggesting that oral tobacco when mixed with lime and betel leaves causes oral cancer in the Indian subcontinent. Similarly, snuff spiced with dried aloe has been reported to cause upper jaw malignancies in the Bantu tribes. The last reported case of nasal snuff causing cancer of the nose was described by John Hill in 1761. We describe here a case of a 69-year-old woman who developed a nasal vestibular malignancy after 30 years of snuff usage, and this, we believe, is the only reported case of nasal snuff causing cancer in the last 2 centuries.

36. Thankappan KR, Thresia CU.

Tobacco use & social status in Kerala.

Indian J Med Res. 2007 Oct;126(4):300-8

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Health indicators of Kerala State such as infant mortality rate (14/ 1000 live births) and life expectancy at birth (71 yr for men and 76 yr for women) are far ahead of the Indian averages (IMR 58, life expectancy men 62 and women 63) and closer to the developed countries. However, tobacco use prevalence is similar to the national average. Smoking is the commonest form of tobacco usage among men in the State whereas chewing tobacco is more common among women and children. Tobacco chewing among men is increasing in Kerala probably due to the smoking ban and industry strategy to focus on smokeless tobacco. Tobacco use is significantly more among the low socio-economic (SE) groups compared to the high SE group. Mortality and morbidity attributed to tobacco is higher among the poorest people in the State. Age adjusted cancer rate of oral cavity and lung cancer has been increasing in the State in recent years. Heart diseases among the young people are increasing in the State. Cancer and heart diseases are chronic illnesses, which may pull the individual and the entire family below the poverty line. Tobacco control therefore should be a top priority not only as a health issue but as a poverty reduction issue. Poverty alleviation is one of the major goals of developing economies. No poverty alleviation programme can ignore the potential impoverishment associated with tobacco use. Kerala with a very strong decentralized government has a very good opportunity to address tobacco control as a priority at the grass root level and reduce the impoverishment due to tobacco use.

37. Varma D, Gupta S, Mandal AK.

Role of p53 and bcl2 as markers of vitamin A response in premalignant lesions of the oral cavity.

Indian J Pathol Microbiol. 2007 Jan;50(1):15-7.

Department of Pathology, Maulana Azad Medical College and L.N. Hospital, New Delhi.

Oral cancer accounts for 40 to 50% of cancers diagnosed in India. Oral cancer is preceded in most cases by pre malignant lesions-leukoplakia, submucous fibrosis and lichen planus. Stoppage of causative agents reverts premalignant lesions in some of the cases only. Thus anti oxidant therapy is being used to revert premalignant change to normal. Few studies available, have taken clinical parameters as indicators of response to therapy. Extensive medline search failed to reveal any study at the cellular level. This study attempts to investigate for the first time the role of p53 and bcl2 as markers of prognosis following vitamin A therapy. 24 cases of pre malignant lesions of oral cavity

were studied. 1 lakh IU of vitamin A were given orally twice a week for 3 months. Biopsies were done before and after therapy. Haematoxylin and Eosin stain was done to confirm diagnosis. Immunostaining for mutant p53 and bcl2 was done on paraffin sections. 500 cells were counted over an average of 5 HPF and percentage positivity was calculated. Statistical analysis was done by applying the paired t tests. In 19 cases (79.2%) of premalignant lesions mutant p53 expression was zero before therapy, and remained unchanged even after the therapy. 3 cases (12.5%) had high mutant p53 values which reduced following therapy ($p = 0.037$). Therapy thus proved effective in these cases. However, in 2 cases (8.3%) pre therapy values of zero showed an increase after vitamin A therapy. These were the cases which had dysplasia and were chronic smokers. In 2 cases (8.3%) pre therapy values of bcl2 were zero and remained unchanged even after therapy and these cases did not stop smoking even during the vitamin A therapy. In 12 cases (50.0%) higher pre therapy values were reduced after therapy ($p < 0.0001$). Vitamin A therapy was effective in these cases. However, in 10 cases (42.0%) expression of bcl2 increased subsequent to therapy. Therapy failed in these cases because of chronic heavy smoking and tobacco chewing. Thus, in the majority of cases vitamin A was effective in preventing mutation of p53 (91.7%) and expression of bcl2 (58.0%). In effect, these two oncoproteins can be used as prognostic markers and follow up for anti oxidant therapy.

38. Vora HH, Mehta SV, Shah KN, Brahmbhatt BV, Desai NS, Shukla SN, Shah PM.

Cytoplasmic localization of BAG-1 in leukoplakia and carcinoma of the tongue: correlation with p53 and c-erbB2 in carcinoma.

Int J Biol Markers. 2007 Apr-Jun;22(2):100-7.

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Background: The present study evaluated the clinical significance of BAG-1, an antiapoptotic protein, in leukoplakia and carcinoma of the tongue.

Methods: BAG-1 expression was evaluated by immunohistochemistry in paraffin-embedded tissues of leukoplakia ($n=25$) and carcinoma of the tongue ($n=61$).

Results: Cytoplasmic expression was predominantly seen in 80% and 70% of patients with leukoplakia and carcinoma, respectively. BAG-1 expression was found to be significantly lower in tobacco users than in non-tobacco users. BAG-1 expression in tobacco-using leukoplakia and carcinoma patients was compared by grouping the carcinoma patients according to lymph node status and disease stage. Carcinoma patients with tumor-positive lymph nodes had significantly lower BAG-1 expression than patients with negative lymph nodes and leukoplakia. Further, a trend towards an inverse correlation was observed with p53 and c-erbB2. In univariate and multivariate survival

analysis, patient subgroups with 2+ or 3+ marker positivity (BAG-1 negativity, p53 and c-erbB2 positivity) had a reduced overall survival compared with patient subgroups with 1+ marker positivity or negativity.

Conclusion: BAG-1 negativity in association with p53 and c-erbB2 positivity identified a subgroup of tongue cancer patients with an aggressive phenotype. Hence, an antiapoptotic protein, BAG-1, was found to be down-regulated in chewing-tobacco-mediated tongue carcinogenesis.

39. Yadav AK, Kaushik CP, Haritash AK, Singh B, Raghuvanshi SP, Kansal A

Determination of exposure and probable ingestion of fluoride through tea, toothpaste, tobacco and pan masala

J Hazard Mater. 2007 Apr 2;142(1-2):77-80.

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Levels of water soluble and acid soluble fluoride in tea, toothpaste, tobacco and pan masala (mouth freshener) were estimated. These items are, generally, ignored while calculating the total dietary intake of fluoride. Tea, toothpaste, tobacco, pan masala (with tobacco and without tobacco) frequently expose human body to 3.88-137.09, 53.5-338.5, 28.0-113.0, 16.5-306.5 and 23.5-185.0 μg of fluoride per gram of these items, respectively. An effort was also made to quantify, on the basis of available studies, the probable human ingestion of fluoride through these substances. Increased leaching of fluoride from some of these substances has been observed in acidic conditions in the present study. The results can be extrapolated to acidic conditions of human stomach.

40. Avti PK, Kumar S, Pathak CM, Vaiphei K, Khanduja KL.

Smokeless tobacco impairs the antioxidant defense in liver, lung, and kidney of rats.

Toxicol Sci. 2006 Feb;89(2):547-53.

Department of Biophysics, Postgraduate Institute of Medical Education and Research, Chandigarh-160012, India

The present study was designed to evaluate the effects of long-term use of aqueous extract of gutkha (a form of smokeless tobacco) on the antioxidant defense status and histopathological changes in liver, lung, and kidney of male Wistar rats. Animals were orally administered aqueous extract of smokeless tobacco (AEST) at a low dose (96 mg/kg body weight per day) for 2 and 32 weeks, and at a high dose (960 mg/kg body weight per day) for 2 weeks. High-dose AEST for 2 weeks decreased the hepatic glutathione (GSH) and glutathione peroxidase (GPx), and increased lipid peroxidation (Lpx) by 17%, 19%, and 20%, respectively. Low-dose AEST for 32 weeks significantly

decreased ($p < 0.05$) the antioxidant status in these organs. In liver, AEST decreased GSH levels and the activities of superoxide dismutase (SOD), catalase (CAT), and GPx by 34.6%, 29%, 17.1%, and 17.4%, respectively, but it increased Lpx by 64%. In kidney, GSH, SOD, CAT, and GPx were decreased by 26.6%, 23%, 33%, and 18%, respectively, with an increase of Lpx by 65%. AEST decreased the lung GSH, SOD, CAT, and GPx, and increased lung Lpx by 43%, 28.5%, 37%, 40%, and 24%, respectively. However, no change in the plasma levels of vitamins A, C, and E were observed with AEST treatment. Histopathological findings suggest that administration of AEST at the high dose for 2 weeks or at the low dose for 32 weeks could cause mild to moderate inflammation in liver and lungs. In conclusion, a decrease in the antioxidant defense system and long-term inflammation caused by smokeless tobacco may be risk factors for gutkha-induced pathogenesis.

41. Ghoshal S, Mallick I, Panda N, Sharma SC.

Carcinoma of the buccal mucosa: analysis of clinical presentation, outcome and prognostic factors.

Oral Oncol. 2006 May;42(5):533-9

Department of Radiotherapy, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Records of 100 consecutive cases of carcinoma of the buccal mucosa treated in our institute between January 2000 and December 2003 were analyzed for clinical presentation, patterns of care, disease-free survival (DFS) and prognostic factors. There were 75 males and 25 females. The mean age was 50 years. Ninety five gave a history of abuse of oral tobacco products. Only 20 patients were in Stage I or II. Sixty one patients had Stage IV disease. Sixty six patients were treated with radical intent while 34 were suitable only for palliative radiation. The 2-year DFS for the entire group was 47.94%. All failures occurred by 12 months. However, the 2-year DFS in radically treated patients was 76.4%. On univariate analysis, late overall stage, T3/T4 disease, node positivity and palliative treatment were significant poor prognostic factors. On multivariate analysis, T3/T4 disease and palliative treatment were independent poor prognostic factors. Early detection can improve outcomes considerably in this disease.

42. Gupta PC, Subramoney S.

Smokeless tobacco use and risk of stillbirth: a cohort study in Mumbai, India.

Epidemiology. 2006 Jan;17(1):47-51

Epidemiology Unit, Tata Institute of Fundamental Research, Mumbai, India.

Background: Maternal cigarette smoking has been causally associated with an increased risk for stillbirth. Preliminary reports suggest an increased risk for stillbirth with smokeless tobacco use during pregnancy.

Methods: We conducted a population-based prospective cohort study to investigate this association by using a house-to-house approach to recruit 1,217 women who were between 3 and 7 months' gestation. Of these, 96% were contacted after delivery to determine the pregnancy outcome. Demographic and maternal variables which were apparently associated either with stillbirth or with smokeless tobacco use ($OR \geq 1.5$) were included as potential confounders. Stillbirth was defined as any delivery of a dead fetus after 20 completed weeks of gestation. We used time-to-event methods to analyze the risk of stillbirth.

Results: Overall occurrence of stillbirth among singleton deliveries in this population was 4.1%. Smokeless tobacco use was reported by 17% of women; 8.9% of smokeless tobacco users had a stillbirth compared with 3.1% among nonusers (life-table adjusted hazard ratio = 3.1; 95% confidence interval = 1.7-5.6). After adjustment by the Cox proportional hazards procedure for age, educational and socioeconomic background, working status of mother, parity, prenatal care variables, and place of delivery, the risk for stillbirth in users was 2.6 (95% confidence interval-1.4-4.8). Most women used mishri (a pyrolyzed tobacco product often used as dentifrice), and there was a dose-response relationship between the daily frequency of use and stillbirth risk. The risk of stillbirth associated with smokeless tobacco use was greater in earlier gestational periods.

Conclusion: Smokeless tobacco use during pregnancy increases stillbirth risk, with a risk at least as great as that associated with maternal cigarette smoking.

43. Jane C, Nerurkar AV, Shirsat NV, Deshpande RB, Amrapurkar AD, Karjodkar FR.

Increased survivin expression in high-grade oral squamous cell carcinoma: a study in Indian tobacco chewers.

J Oral Pathol Med. 2006 Nov;35(10):595-601

Department of Biochemistry, T N Medical College, B Y L Nair Hospital, Mumbai.

Background: Oral cancer is one of the five leading sites of cancer in the Indian population. In the present study we analyzed the expression of apoptosis regulating genes, viz. survivin, Bcl-2, Bax and p53 in precancerous and cancerous lesions of the buccal mucosa of Indian tobacco chewers.

Methods: Paraffin-embedded tissue samples from 38 patients with primary oral squamous cell carcinoma (OSCC) and 17 patients with leukoplakia were used. The expression of survivin, Bcl-2, Bax, and p53 was evaluated using immunohistochemical staining method.

Results: 36% percent OSCC were found to be positive for nuclear p53 staining while none of the precancerous lesions showed p53 positivity. Survivin, Bcl-2 and Bax

expression was found to increase with increased grade of malignancy. Increase in survivin expression was statistically most significant ($P < 0.001$).

Conclusion: Increased expression of anti-apoptotic survivin in high-grade tumors suggests that survivin is likely to contribute significantly to apoptosis resistance in response to therapy.

44. Kar P, Supakar PC.

Expression of Stat5A in tobacco chewing-mediated oral squamous cell carcinoma.

Cancer Lett. 2006 Aug 28;240(2):306-11

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Oral squamous cell carcinoma (oscc) is the fifth most common cancer worldwide and the number of cases is increasing regularly in the developing world. The effective detection of oscc at its early stages becomes necessary for proper treatment due to limited understanding of the critical pathways during oncogenesis. Signal transducer and activators of transcription (Stats) are an important group of transcription factors, which contribute to tumorigenesis due to their intimate connection to growth factor signalling, apoptosis, and angiogenesis. They also play a critical role in immune responses and hence defective Stat signalling could favour tumour development by compromising immune surveillance. The role of Stat5A in mammary gland carcinoma and leukaemia has already been reported. We for the first time report here the constitutive activation of Stat5A as one of the early events in tobacco mediated-oscc in the eastern Indian population, which can be used as a potent prognostic molecular marker.

45. Kumar S, Pandey U, Bala N, Tewari V, Oanh KT.

Tobacco habit in northern India.

J Indian Med Assoc. 2006 Jan;104(1):19-22, 24.

Department of Surgery, King George's Medical College, Lucknow 226003.

To study tobacco consumption practices in north-Indian population, a community-based, stratified sampling survey using validated interview schedule was performed in rural/urban areas of Lucknow, Uttar Pradesh. There were 432 tobacco users (385 men, 47 women; 276 urban, 156 rural) taken as subjects. Tobacco use practices ie, chewing/smoking/rubbing/snuffing, frequency, starting age, supply, place/context of use, quid habit, affect, facilitating conditions/barriers, tobacco users' opinion on control measures were all taken into consideration. Single mode of tobacco use was reported by 277 subjects (64.1%) and the rest had a plethora of tobacco practices. Chewing was prevalent in 322(74.5%), smoking in 256(59.3%), rubbing in 32(7.4%) and snuffing in 4 subjects (0.9%). Of the 10 preparations in the questionnaire, the "top 5" preferences

ranked as tobacco-betel, gutka, cigarette, bidi and khaini that remained unchanged between sexes, rural/urban people and age groups. Women significantly ($p < 0.00001$) preferred smokeless tobacco and perceived social barrier for smoking. Gutka consumption was significantly higher in youngsters (< 25 years; $p < 0.0001$). Most subjects (235; 54.3%) used tobacco 7-24 times/day. Majority (259; 60%) users started consuming tobacco before 21 years of age and about a fifth 95(22%) before 15 years. Majority users (232; 53.6%) did not procure tobacco from a fixed shop. The commonest context of tobacco use was with any refreshment (337; 78.0%). Of the 322 tobacco chewers, about half the subjects (178; 52.2%) rotated the quid in their mouth, 313(97.2%) later spat it out, 9(2.1%) swallowed it and 15(4.7%) admitted to sleep with the quid in mouth. Tobacco along with alcohol was consumed by 82(19%) and with opium by 33 subjects (7.6%). Social barrier to tobacco use was perceived by 231 subjects (53.5%), especially by smokers. Majority users (355; 82.2%) did not have negative feelings or embarrassment in using tobacco. Most users (351; 81.4%) said they would welcome legislative control on tobacco use.

46. Manchanda P, Sharma SC, Das SN.

Differential regulation of IL-2 and IL-4 in patients with tobacco-related oral squamous cell carcinoma.

Oral Dis. 2006 Sep;12(5):455-62.

Department of Biotechnology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi- 110 029, India.

Aim: The aim of the study was to investigate the systemic immunity in terms of major lymphocyte subsets and the expression of IL-2 and IL-4 in T-cell subsets from peripheral blood of patients with tobacco-related intraoral squamous cell carcinoma.

Methods: CD3+, CD4+ and CD8+ T-cell subsets and CD16+ CD56+ natural killer cells, and intracellular cytokines in T-cell subsets were determined by two-colour flow cytometry and confocal microscopy.

Results: Oral cancer patients showed a significantly reduced ($P < 0.001$) CD3+ and CD4+ T-cell subsets with a lower CD4/CD8 ratio when compared with the normal controls. The frequency of CD3+, IL-4+ and CD8+ IL-4+ T cells were significantly higher ($P < 0.001$) while CD4+ IL-2+ were significantly lower ($P < 0.02$) in patients when compared with the normal controls. Late stage of the tumour was associated with reduced expression of IL-2 in both CD4+ ($P < 0.05$) and CD8+ ($P < 0.03$) subsets.

Conclusions: The tobacco-related intraoral squamous cell carcinoma seems to be associated with multiple systemic immune defects particularly, an impaired CD3+ and CD4+ T cells in the peripheral blood as well as a differential regulation of IL-2 and IL-4 in CD4+ and CD8+ T-cell subsets. The cytokine response in these patients seems to be

skewed from protective Th1 to immunosuppressive Th2 type. Thus these patients could be ideal candidate for immunomodulation therapy.

47. Pai SB, Pai RB, Lalitha RM, Kumaraswamy SV, Lalitha N, Johnston RN, Bhargava MK.

Expression of oncofoetal marker carcinoembryonic antigen in oral cancers in South India--a pilot study.

Int J Oral Maxillofac Surg. 2006 Aug;35(8):746-9.

Kidwai Memorial Institute of Oncology, Hosur Road, Bangalore, India.

Expression of the oncofoetal glycoprotein, carcinoembryonic antigen (CEA), has been observed in a number of malignancies and is also being pursued as a target for anti-cancer therapy. This study explored the status of this biochemical entity in the oral squamous cell carcinoma (SCC) in South India caused by extensive chewing habits. Squamous cell carcinoma in the study belonged to grade I and grade II. Tumour staging of the patients recruited in the study ranged from T2N1M0 to T4N3M0. Of the grade II cases studied, 88% (7 out of 8) showed expression of CEA. The 2 cases of grade I SCC of buccal mucosa also showed positive anti-CEA staining. If the results from this pilot study can be validated with a larger sample size, a role can be attributed to this tumour marker in oral neoplasia, thereby opening up avenues for using CEA as an additional diagnostic marker in oral SCC in this population and as a possible target for anti-cancer therapy.

48. Pednekar MS, Gupta PC, Shukla HC, Hebert JR.

Association between tobacco use and body mass index in urban Indian population: implications for public health in India.

BMC Public Health. 2006 Mar 16;6:70

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Background: Body mass index [BMI, weight (kg)/height (m²)], a measure of relative weight, is a good overall indicator of nutritional status and predictor of overall health. As in many developing countries, the high prevalence of very low BMIs in India represents an important public health risk. Tobacco, smoked in the form of cigarettes or bidis (handmade by rolling a dried rectangular piece of temburni leaf with 0.15-0.25 g of tobacco) or chewed, is another important determinant of health. Tobacco use also may exert a strong influence on BMI.

Methods: The relationship between very low BMI (< 18.5 kg/m²) and tobacco use was examined using data from a representative cross-sectional survey of 99,598 adults (40,071 men and 59,527 women) carried out in the city of Mumbai (formerly known as

Bombay) in western India. Participants were men and women aged ≥ 35 years who were residents of the main city of Mumbai.

Results: All forms of tobacco use were associated with low BMI. The prevalence of low BMI was highest in bidi-smokers (32% compared to 13% in non-users). For smokers, the adjusted odds ratio (OR) and 95% confidence interval (CI) were OR = 1.80(1.65 to 1.96) for men and OR = 1.59(1.09 to 2.32) for women, respectively, relative to non-users. For smokeless tobacco and mixed habits (smoking and smokeless tobacco), OR = 1.28(1.19 to 1.38) and OR = 1.83(1.67 to 2.00) for men and OR = 1.50(1.43 to 1.59) and OR = 2.19(1.90 to 3.41) for women, respectively.

Conclusions: Tobacco use appears to be an independent risk factor for low BMI in this population. We conclude that in such populations tobacco control research and interventions will need to be conducted in concert with nutrition research and interventions in order to improve the overall health status of the population.

49. Raju P, George R, Ve Ramesh S, Arvind H, Baskaran M, Vijaya L.

Influence of tobacco use on cataract development.

Br J Ophthalmol. 2006 Nov;90(11):1374-7.

Medical Research Foundation, Sankara Nethralaya, 18 College Road, Chennai, India 600006.

Aim: To study the influence of tobacco use on cataract formation in a rural South Indian population.

Methods: 3924 subjects from the Chennai Glaucoma Study conducted in rural south India underwent a comprehensive eye examination, including Lens Opacities Classification System II grading. Information on tobacco use, type of tobacco (smoking and smokeless), duration and quantity of use was collected.

Results: 1705 (male:female (M:F) 1106:599) people used tobacco and were significantly older (mean (standard deviation (SD)) age 55.80 (10.64) years) than non-users (52.23 (10.51); $p < 0.001$). 731 (M:F 730:1) people smoked, 900 (M:F 302:598) used smokeless tobacco, and 74 (M:F, 74:0) used tobacco in both forms. The unadjusted and adjusted (age and sex) odds ratio (OR) for a positive history of tobacco use and cataract was 1.72 (95% confidence interval (CI) 1.51 - 1.96) and 1.39 (95% CI 1.15 - 1.68), respectively. The unadjusted OR for smokers and smokeless tobacco users was 1.04 (95% CI 0.88 - 1.23) and 2.74 (95% CI 2.31 - 3.26), respectively. The adjusted OR was 1.19 (95% CI 0.89 - 1.59) and 1.54 (95% CI 1.22- 1.95), respectively. No significant association was noted between smoking and any particular type of cataract. Smokeless tobacco use was found to be significantly associated with nuclear cataract even after adjusting for age and sex (OR 1.67, $p = 0.067$, 95% CI 1.16- 2.39).

Conclusions: Tobacco use was significantly associated with cataract. Smoking was not found to be significantly associated with cataract formation; however, smokeless tobacco use was more strongly associated with cataract.

50. Ramachandran S, Ramadas K, Hariharan R, Rejnish Kumar R, Radhakrishna Pillai M.

Single nucleotide polymorphisms of DNA repair genes XRCC1 and XPD and its molecular mapping in Indian oral cancer.

Oral Oncol. 2006 Apr;42(4):350-62.

Department of Molecular Medicine, Regional Cancer Centre, Thiruvananthapuram 695 011, India.

Tobacco users with diminished ability to repair somatic mutations may be more susceptible to tobacco attributable cancers. The distribution of single nucleotide polymorphisms (SNPs) in DNA repair genes XRCC1 and XPD in 110 oral carcinoma cases, 84 leukoplakia and 110 controls belonging to the Travancore South Indian population were examined. SNPs investigated included Arg194Trp, Arg280His, and Arg399Gln of the XRCC1 gene and Lys751Gln of the XPD gene. In addition, one of the variants positions, A399G, was mapped onto the BRCT I domain model built by comparative modeling (threading). Presence of the polymorphic variant of XRCC1 codon 194 and 399 and XPD was associated with increased risk of oral cancer compared to the wild genotype. Smokers and betel quid chewers with the variant allele of XRCC1 399 codon and XPD also exhibited increased risk of oral cancer. The A399G variant position mapped onto the surface of the BRCT I domain provides a possible rationale for altered XRCC1 function. These results suggest that polymorphisms in functionally important repair genes, specifically, those that map onto the protein surface may alter protein function without significantly affecting its structure.

51. Rohatgi N, Matta A, Kaur J, Srivastava A, Ralhan R.

Novel molecular targets of smokeless tobacco (khaini) in cell culture from oral hyperplasia.

Toxicology. 2006 Jul 5;224(1-2):1-13.

Department of Biochemistry, All India Institute for Medical Sciences, Ansari Nagar, New Delhi 110 029, India.

Knowledge of molecular mechanism(s) implicated in smokeless tobacco (ST) associated oral carcinogenesis is meager. In an attempt to identify genes that are modulated by ST, we recently reported establishment of an oral epithelial cell culture, AMOL III from oral hyperplasia with hyperkeratosis of a khaini consumer. Herein we aimed to identify novel molecular targets of ST (khaini) in AMOL III cells using differential display. Fourteen novel differentially expressed genes (12 upregulated and 2 downregulated) were identified. These differentially expressed cDNAs were amplified, cloned, sequenced and confirmed by reverse northern blotting. Mainly these genes are components of transcriptional machinery, cell-cell adhesion, signaling, growth and transformation processes. The important novel molecular targets identified included activated leucocyte cell adhesion molecule (ALCAM), CDP-diacylglycerol-inositol 3-phosphatidyl transferase (phosphatidylinositol synthase), CDIPT, an important enzyme in phosphatidyl inositol

biosynthesis, ribosomal protein (RPS23), KIAA0121 and growth and transformation factor, E2IG5. Semi-quantitative RT-PCR analysis of these five genes confirmed over-expression of these genes in oral pre-malignant lesions (OPLs) and oral squamous cell carcinomas (OSCCs) of ST consumers underscoring their biological relevance in ST-associated oral tumorigenesis. In depth studies are warranted to determine the functional significance of ALCAM and CDIPT in oral carcinogenesis.

52. Samal IR, Maneesh M, Chakrabarti A.

Evidence for systemic oxidative stress in tobacco chewers.

Scand J Clin Lab Invest. 2006;66(6):517-22

Department of Biochemistry, Amrita Institute of Medical Sciences, Kochi, India.

Objective: To evaluate erythrocyte malondialdehyde (MDA) levels and activities of superoxide dismutase (SOD) and glutathione reductase (GR) in tobacco chewers, in view of possible oxidative stress in oral smokeless tobacco.

Materials and methods: 60 healthy male tobacco chewers, aged 30.6 ± 4.7 years with a 3 to 10-year (7.37 ± 2.1) history of tobacco chewing, were included in the study. 32 healthy male volunteers, aged 26.5 ± 4.8 years, served as controls. All the participants were from the same community and of similar dietary habits.

Results: The erythrocyte MDA level and activities of erythrocyte SOD and GR were estimated. There was a significant duration- (tobacco chewing) dependent increase in erythrocyte MDA levels along with a significant duration- (tobacco chewing) dependent decrease in erythrocyte SOD and GR activity.

Conclusion: Oral smokeless tobacco causes a duration-dependent increase in oxidative stress.

53. Saraswathi TR, Ranganathan K, Shanmugam S, Sowmya R, Narasimhan PD, Gunaseelan R.

Prevalence of oral lesions in relation to habits: Cross-sectional study in South India.

Indian J Dent Res. 2006 Jul-Sep;17(3):121-5

Department of Oral and Maxillofacial Pathology, Ragas Dental College and Hospital, Chennai, India.

Background: Smoking, drinking and chewing tobacco product, common habits in India have been positively associated with oral lesions. No study has been conducted in this part of Tamilnadu regarding the prevalence of oral lesions in relation to habits.

Methods: A hospital based cross-sectional study was carried out at Ragas Dental College, Chennai. Already existing data of two thousand and seventeen consecutive patients from sub-urban areas of Chennai, who attended the outpatient department, at Ragas Dental College, for dental complaints during a period of three months in 2004, who underwent oral examination and interviewer based questionnaire was used.

Results: Oral soft tissue lesions were found in 4.1% of the study subjects. The prevalence of leukoplakia, OSF and oral lichen planus was 0.59%, 0.55%, and 0.15% respectively. The prevalence of smoking, drinking alcoholic beverages and chewing was 15.02%, 8.78% and 6.99% respectively. Smoking and chewing were significant predictors of leukoplakia in this population.

Discussion: The prevalence of leukoplakia, OSF and oral lichen planus in our study population is similar to those found in other populations. The prevalence of consumption of alcoholic beverages in our study population was higher when compared to the Indian National Sample Survey study. However the prevalence of smoking and chewing was found to be lower. Smokers were more likely to develop smoker's melanosis compared to other lesions. Among those who consumed alcoholic beverages alone, the prevalence of leukoplakia was higher compared to other lesions. OSF was the most prevalent lesion among those who chewed panmasala or gutkha or betel quid with or without tobacco.

54. Sharma C, Kaur J, Shishodia S, Aggarwal BB, Ralhan R.

Curcumin down regulates smokeless tobacco-induced NF-kappaB activation and COX-2 expression in human oral premalignant and cancer cells.

Toxicology. 2006 Nov 10;228(1):1-15.

Department of Biochemistry, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

Smokeless tobacco (ST) consumption is a major cause of oral cancer in South East Asia including India. Recently, we showed that exposure to smokeless tobacco extract (STE) (khaini) results in increased expression and activation of nuclear factor-kappaB (NF-kappaB) and its downstream target cyclooxygenase-2 (COX-2) in human oral cell systems in vitro. The present study was designed to test the hypothesis that curcumin may inhibit the activation of NF-kappaB in ST exposed oral premalignant and cancer cells. Exposure of oral premalignant and cancer cells to curcumin resulted in significant decrease in cell viability and induced apoptosis. STE-induced nuclear translocation and DNA-binding activity of NF-kappaB were inhibited in curcumin pretreated oral premalignant and cancer cells in vitro. Curcumin treatment led to decreased expression of NF-kappaB and COX-2. The tobacco specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), is one of the carcinogenic components of STE (khaini). We demonstrate that curcumin pretreatment abrogated NNK-induced activation of NF-kappaB and COX-2 expression, suggesting that NNK is one of the factors in STE (khaini) modulated by curcumin. In conclusion, our findings demonstrate for the first time that curcumin downregulates STE (khaini) or NNK-induced NF-kappaB and COX-2 in oral premalignant and cancer cells in vitro.

55. Tiwari R, Deb P, Debbarma A, Chaudhuri R, Chakraborty A, Lepcha M, Chakraborty G.

Tobacco use and cardiovascular disease: a knowledge, attitude and practice study in rural Kerala.

Indian J Med Sci. 2006 Jul;60(7):271-6

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Background: Tobacco consumption, either in smokeless form or as smoking, is reported to be responsible for major non-communicable diseases, namely, cardiovascular diseases, chronic obstructive pulmonary diseases and cancers. Whatsoever control strategy is being used, the community participation is of utmost importance, which will depend largely on the level of the knowledge in the community. **AIM:** To assess the knowledge and attitude of a rural community towards the harmful effects of tobacco use.

Setting and design: Venganoor Gram Panchayat of Thiruvananthapuram district of Kerala; cross-sectional study.

Materials and methods: Interview schedule was used to collect the information on pre-designed and pre-tested proforma. The information recorded, included the demographic characteristics and socio-economic characteristics. The awareness regarding tobacco use and the attitude towards its non-usage was done, by putting forward, open and closed-ended questions.

Statistical analysis: Percentages and proportions; t-test; chi-square test.

Results: The present study included 302 (64.7%) females and 165 (35.3%) males. Among the males, 44 (38.5%) were ever smokers. Though 451 (96.6%) of the subjects knew that tobacco use is harmful for health, only 101 (22.5%) of the subjects knew that it causes cardiovascular diseases. Electronic and print media were the common source of such knowledge being reported by 265 (58.7%) and 202 (44.7%) subjects, respectively.

Conclusions: The subjects were aware about the harmful effects of tobacco use. However, more efforts are needed to make them aware about the role of tobacco smoking and chewing, in causing cardiac problems.

56. Einstein TB, Sivapathasundharam B.

Cytomorphometric analysis of the buccal mucosa of tobacco users.

Indian J Dent Res. 2005 Apr-Jun;16(2):42-6.

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Objectives: This study has been carried out to assess the effect of tobacco smoking and of betel quid chewing with tobacco on buccal mucosa by cytomorphometry, in a south Indian population.

Study design: Cellular diameter (CD) and nuclear diameter (ND) of exfoliated buccal squames obtained from clinically normal appearing buccal mucosa of tobacco smokers, betel quid with tobacco chewers, and those with a combined habit, stained by the Papanicolaou method, were measured. Non-users served as negative controls and oral squamous cell carcinomas in tobacco users served as positive controls. One way ANOVA test of the values obtained followed by multiple range comparison with Tukey-HSD procedure (at $p=0.05$) was carried out.

Results: A statistically significant reduction in CD and increase in ND in smokers and those with a combined habit were observed.

Conclusions: The use of tobacco in the form of smoking influences the cytomorphology of buccal mucosa.

57. Gupta PC, Pednekar MS, Parkin DM, Sankaranarayanan R.

Tobacco associated mortality in Mumbai (Bombay) India.

Results of the Bombay Cohort Study.

Int J Epidemiol. 2005 Dec;34(6):1395-402.

Healis, Sekhsaria Institute for Public Health, 601/B, Great Eastern Chambers, Plot No. 28, Sector 11, CBD Belapur, India.

Background: Little is known about the excess mortality from forms of tobacco use other than cigarette smoking that are widely prevalent in India, such as bidi smoking and the various forms of smokeless tobacco use. We report on absolute and relative risks of mortality among various kinds of ever tobacco users vs never-users in the city of Mumbai, India.

Methods: Using the Mumbai voters' list as the selection frame, 99 570 individuals aged ≥ 35 years were interviewed at their homes during 1992-94. At active follow-up (during 1997-99) after 5.5 years, 97 244 (97.7%) were traced. Among these, 7531 deaths (4119 men, 3412 women) were recorded, of which 89% died within study area. It was possible to abstract cause of death information from the records of the municipal corporation for 5470 deaths. These were coded using ICD 10.

Results: The adjusted relative risk was 1.37 (95% CI 1.23-1.53) for (men) cigarette smokers and 1.64 (95% CI 1.47-1.81) for bidi smokers, with a significant dose-response relationship for number of bidis or cigarettes smoked. Women were essentially smokeless tobacco users; the adjusted relative risk was 1.25 (95% CI 1.15-1.35). The risk of deaths from respiratory diseases (RR 2.12, 95% CI 1.57-2.87), tuberculosis (RR 2.30, 95% CI 1.68-3.15), and neoplasms (RR 2.60, 95% CI 1.78-3.80) were significantly high in male smokers than never tobacco users.

Conclusions: Bidi is no less hazardous than cigarette smoking, and smokeless tobacco use may also result in significantly increased mortality.

58. Kaur R, Nagpal JK, Das BR.

Polymorphism in IGF-2 as a surrogate marker for predisposition towards tobacco chewing-mediated oral cancer.

Tumour Biol. 2005 May-Jun;26(3):147-52.

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Insulin and insulin-like growth factors (IGFs) are major determinants of proliferation and apoptosis, thereby playing a significant role in carcinogenesis. Epidemiological evidence associates high levels of INS and IGFs with an increased risk of cancer. Polymorphism of the genes involved in insulin-signaling pathways has been associated with a variable risk for neoplasms in different ethnic and environmental backgrounds. In this study, using PCR-RFLP-based assays, we investigated the distribution of genetic polymorphism in INS and IGF-2 genes in tobacco chewing-mediated oral cancer patients (n = 60) and healthy controls (n = 45) of Indian ethnic origin. The genotyping was performed for +1127 INS-Pst1 in INS and +3580 IGF-2-Msp1 in IGF-2. The frequencies of the IGF-2 genotypes AG, GG and AA found in oral cancer patients were 0.68, 0.2 and 0.12, respectively, whereas in noncancer controls these frequencies were 0.27, 0.71 and 0.02. Frequencies of each allele, i.e. CT, TT and CC of INS gene, were found to be nearly equal in the tumor (0.22, 0.75 and 0.03) as well as the normal (0.27, 0.67 and 0.06) population. A significant difference was observed in genotypic frequencies of IGF-2 and INS in the Indian ethnic population as compared to the Caucasian, African and Hispanic populations. Polymorphism at +1127 INS-Pst1 locus of INS gene does not show an implication in oral cancer, whereas the genotype AG or AA at +3580 IGF-2-Msp1 locus of IGF-2 is associated with progression and increased risk of oral cancer. From our study we can conclude that single nucleotide polymorphisms in the IGF-2 gene can be used as a marker for prediction of the risk of oral carcinogenesis.

59. Majumder M, Sikdar N, Paul RR, Roy B.

Increased risk of oral leukoplakia and cancer among mixed tobacco users carrying XRCC1 variant haplotypes and cancer among smokers carrying two risk genotypes: one on each of two loci, GSTM3 and XRCC1 (Codon 280).

Cancer Epidemiol Biomarkers Prev. 2005 Sep;14(9):2106-12.

Human Genetics Unit, Indian Statistical Institute, Kolkata.

An individual's susceptibility to oral precancer and cancer depends not only on tobacco exposure but also on the genotypes/haplotypes at susceptible loci. In this hospital-based case-control study, 310 cancer patients, 197 leukoplakia patients, and 348 controls were studied to determine risk of the disease due to polymorphisms at three sites on XRCC1 and one site on XRCC3. Independently, variant genotypes on these loci did not

modulate risk of leukoplakia and cancer except for the XRCC1 (codon 280) risk genotype in exclusive smokeless tobacco users with leukoplakia [odds ratios (OR), 2.4; 95% confidence intervals (CI), 1.0-5.7]. But variant haplotypes, containing one variant allele, on XRCC1 increased the risk of leukoplakia (OR, 1.3; 95% CI, 1.0-1.7). Among stratified samples, mixed tobacco users, carrying variant haplotypes, also had increased risk of both leukoplakia (OR, 2.2; 95% CI, 1.3-3.9) and cancer (OR, 1.9; 95% CI, 1.2-3.1). In a previous study on this population, it was shown that the GSTM3 (A/A) genotype increased the risk of oral leukoplakia and cancer among smokers, which has also been substantiated in this study with expanded sample sizes. The simultaneous presence of two risk genotypes in smokers, one on each of two loci, GSTM3 and XRCC1 (codon 280), increased the risk of cancer (OR, 2.4; 95% CI, 1.0-5.8). Again, smokers carrying two risk genotypes, one on each of two loci, GSTM3 and XRCC1 (codon 399), were also overrepresented in both leukoplakia and cancer populations ($P(\text{trend}) = 0.02$ and 0.04 , respectively) but enhancement of risks were not observed; probably due to small sample sizes. Therefore, the presence of variant haplotypes on XRCC1 and two risk genotypes, one on each of two loci, GSTM3 and XRCC1, could be useful to determine the leukoplakias that might progress to cancer in a group of patients.

60. Mehrotra R, Singh M, Gupta RK, Singh M, Kapoor AK.

Trends of prevalence and pathological spectrum of head and neck cancers in North India.

Indian J Cancer. 2005 Apr-Jun;42(2):89-93

Department of Pathology, Moti Lal Nehru Medical College, Allahabad, India.

Background: Head and neck neoplasia constitute one of the commonest cancers in India. Use of smokeless tobacco (Pan masala, Zarda etc.) is on the increase in North India, especially in Uttar Pradesh, and is responsible for the large majority of these tumours.

Aim: To assess the patients' characteristics, yearly prevalence and histopathological subtypes of the head and neck neoplasia (excluding oral cavity) in Allahabad and surrounding regions.

Setting and designs: A retrospective study of 11 years from 1990 to 2000 was designed. Data was collected year-wise using the tumor registry data.

Material and method: All biopsies submitted for histopathology to the Pathology department were reviewed and analyzed for demographic data, site and diagnosis.

Statistical analysis: The Kolmogorov-Smirnov Two-Sample Test was utilized to determine whether two distributions are the same.

Results: A total of 40559 biopsies were examined in the department, of which, lesions of the head and neck region, excluding the oral cavity, constituted 694 biopsies (409 males and 285 females). One hundred and forty-four malignant lesions were reported, 114

being males and 30 females. A comparison of the age-specific prevalence rates of cancer during the study period showed that the prevalence was highest in patients belonging to the 50-59 years age group and squamous cell carcinoma Grade II was the most prevalent type. On an average, 58 new biopsies per annum were received.

Conclusions: Properly structured site-specific data like this can augment the National Cancer Registry Programme and is an essential indicator for the magnitude and the pattern of the cancer problem in India.

61. Mishra R, Das BR.

Activation of STAT 5-cyclin D1 pathway in chewing tobacco mediated oral squamous cell carcinoma.

Mol Biol Rep. 2005 Sep;32(3):159-66

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Cyclin D1 overexpression and upregulation has been reported largely in Oral Squamous Cell Carcinoma (OSCC) but the mechanism behind it is not clear. Here, the transcription and translational upregulation of cyclin D1 was observed in most of the tobacco chewing oral cancer patients where as the gene amplification was limited to only small group (20%) of patients. A transcription factor (TF) binding site has been detected from -483 to -451 by using DNase I foot printing analysis and confirmed by electrophoretic mobility shift assay by using oral tumour nuclear extract (NE). This is a STAT binding sequence and confirmed as STAT 5a by super shift assay. The binding of STAT 5 was observed in 80% (24/30) oral cancer samples. The co-expression of cyclin D1 with STAT 5 binding was observed in 90% (27/30) of the samples. STAT family of proteins is emerging to play role in oral carcinogenesis. Here, the binding of STAT 5 might up regulate cyclin D1 in most of the samples whereas; the gene amplification events are sporadic in oral carcinogenesis. Our study provides the first evidence of the constitutive activation of STAT 5-cyclin D1 pathway in chewing tobacco mediated OSCC.

62. Pathak KA, Gupta S, Talole S, Khanna V, Chaturvedi P, Deshpande MS, Pai PS, Chaukar DA, D'Cruz AK.

Advanced squamous cell carcinoma of lower gingivobuccal complex: patterns of spread and failure.

Head Neck. 2005 Jul;27(7):597-602

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Background: Carcinoma of the gingivobuccal complex is commonly associated with the use of smokeless tobacco known as "quid."

Methods: We conducted a retrospective chart review of 511 patients with advanced cancer of gingivobuccal complex surgically treated during 1994 to 1995. We evaluated patterns of disease failure in these patients and correlated disease-free survival with various prognostic factors.

Results: During a median follow-up of 46 months, 159 locoregional recurrences and 11 distant metastases were detected in 148 patients. Seventy-nine percent of the recurrences appeared within 18 months of surgery, and the median survival for patients with recurrent disease was less than 4 months. Two-year and 5-year disease-free survival rates were 64% and 57%, respectively. On multivariate analysis, disease-free survival showed significant correlation with skin involvement and extracapsular spread.

Conclusions: Gingivobuccal cancers usually fail locoregionally. Soft tissue infiltration and extracapsular spread of nodal disease influence disease-free survival.

63. Phukan RK, Zomawia E, Narain K, Hazarika NC, Mahanta J.

Tobacco use and stomach cancer in Mizoram, India.

Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1892-6.

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The incidence of stomach cancer in India is lower than that of any other country around the world. However, in Mizoram, one of the north-eastern state of India, a very high age-adjusted incidence of stomach cancer is recorded. A hospital-based case-control study was carried out to identify the influence of tobacco use on the risk of developing stomach cancer in Mizoram. Among the cases, the risk of stomach cancer was significantly elevated among current smokers [odds ratio (OR), 2.3; 95% confidence interval (95% CI), 1.4-8.4] but not among ex-smokers. Higher risks were seen for meiziol (a local cigarette) smokers (OR, 2.2; 95% CI, 1.3-9.3). The increased risk was apparent among subjects who had smoked for ≥ 30 years. The increased risk was significant with 2-fold increase in risk among the subjects who smoked for ≥ 11 pack-years. The risk increased with increasing cumulative dose of tobacco smoked (mg). Tuibur (tobacco smoke-infused water), used mainly in Mizoram, was seemed to increased the risk of stomach cancer among current users in both univariate and multivariate models (OR, 2.1; 95% CI, 1.3-3.1). Tobacco chewer alone (OR, 2.6; 95% CI, 1.1-4.2) showed significant risk. Tobacco use in any form [smoking and smokeless (tuibur and chewing)] increased the risk of stomach cancer in Mizoram independently after adjusting for confounding variables.

64. P. S. Chandra, M. P. Carey, K. B. Carey, K. R. Jairam, N. S. Girish , H. P. Rudresh

Prevalence and correlates of tobacco use and nicotine dependence among psychiatric patients in India

Addict Behav. 2005 Aug;30(7):1290-9.

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Tobacco use among psychiatric patients in developing countries has not been well-investigated. To address this issue, we screened consecutive admissions to a major psychiatric hospital in southern India, and assessed the prevalence and correlates of tobacco use and nicotine dependence. Patients (n=988) provided information about their use of tobacco products, and participated in an interview that included the Fagerstrom Test for Nicotine Dependence as well as measures of other substance use. Three hundred and fifty-one patients (36%) reported current tobacco use, with 227 (65% of all users) reporting moderate to severe nicotine dependence. Current tobacco use as well as nicotine dependence were associated with male gender, a diagnosis of bipolar disorder, and risk of other substance use problems. The cultural context of these findings, and the implications for tobacco control among psychiatric patients, are discussed.

65. R. M. John

Tobacco consumption patterns and its health implications in India

Health Policy. 2005 Feb;71(2):213-22.

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The main objective of this paper is to analyze the pattern of tobacco consumption and its health implications in India. We use various rounds of National Sample Survey for this purpose. The paper finds that, though there is a reduction in tobacco consumption in the form of bidi and cigarette in India as a whole, this decrease is compensated for by an increase of pan consumption in rural India. It has also been observed that the consumption of tobacco is more among the poor in India and we argue that the consequent higher health care spending arising out of tobacco related diseases leaves them economically worse off. Thus the paper concludes that, apart from the economic gains that tobacco industry is generating, tobacco use also imposes burden, especially on users, in the form of numerous tobacco related diseases and high health care spending. This, coupled with the fact that the investment on health by government is declining over the years, has the potential to trap the poor in a vicious circle of poverty and ill health. Hence government policy needs to be targeted towards an effective control of tobacco use.

66. Rohatgi N, Kaur J, Srivastava A, Ralhan R.

Smokeless tobacco (khaini) extracts modulate gene expression in epithelial cell culture from an oral hyperplasia.

Oral Oncol. 2005 Sep;41(8):806-20

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Smokeless tobacco (ST) usage is a growing public health problem worldwide. Exposure to smokeless tobacco is carcinogenic to humans. The molecular mechanism(s) underlying ST associated oral carcinogenesis remain largely unknown. The major challenge is to identify the key factor(s) involved in malignant transformation of oral lesions. Knowledge of these factors will provide candidate diagnostic biomarkers and targets for early intervention. To identify the molecular targets in ST associated oral lesions, we established and purified cultures of epithelial cells (AMOL-III) from an oral leukoplakia with histological evidence of hyperplasia with hyperkeratosis from gingivo-buccal sulcus of a smokeless tobacco (khaini) consumer. Cell cultures were characterized and modulation of gene expression in response to smokeless tobacco extract (STE) was investigated using confocal microscopy and immunoblotting. AMOL-III cells showed altered expression of cell cycle regulators namely p53, p21waf1/cip1, hdm2, proliferation marker Ki67 and transcription factor Ets-1. These cells did not harbor HPV 16/18. No mutation was detected in H-Ras codon 12/13 or in p53 exons 5-9 in AMOL-III cells. STE treatment of these cells resulted in loss of pRb, RARbeta, p21 waf1/cip1 and O6-methyl guanine-DNA methyl transferase (MGMT) while the expression of cyclin D1 was increased. To our knowledge this is the first report to demonstrate that khaini modulates expression of multiple cellular targets including proteins involved in cell cycle regulation and DNA methylation, which may lead the oral epithelial cells down the carcinogenic pathway. This in vitro model system assumes importance in unraveling the cellular and molecular mechanisms implicated in smokeless tobacco associated early oral cancer progression.

67. S. Mohan, P. Sankara Sarma, K. R. Thankappan

Access to pocket money and low educational performance predict tobacco use among adolescent boys in Kerala, India

Prev Med. 2005 Aug;41(2):685-92.

Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695 011, India.

Background: Tobacco use is increasing among adolescents. We conducted this study to find prevalence and correlates of tobacco use among adolescent boys in Trivandrum city, Kerala.

Methods: Using a two-stage cluster sampling technique, 1323 boys (12-19 years) were selected from 14 schools. Information on tobacco use, academic performance, pocket

money, and other variables was collected using a questionnaire. Multivariate analyses were done to find associations between current use of tobacco and other variables.

Results: Prevalence of current tobacco use was 11.3% (95% CI 9.6-13.0). Current tobacco use was 2.9 times higher among older boys compared to younger boys (OR 2.9, CI 1.6-5.3), 2 times higher among boys whose fathers used tobacco (OR 2.0, CI 1.3-3.1), 2.9 times higher among boys whose friends used tobacco (OR 2.9, CI 1.6-5.1) compared to their counterparts, 3 times higher among boys securing poor (<40% marks) grade compared to those securing excellent (>80% marks) grade (OR 3.0, CI 1.4-6.6), and 4 times higher among those who received pocket money compared to those who did not (OR 4.0, CI 2.2-7.4).

Conclusions: Health programs to quit tobacco are suggested in schools with special emphasis on poor performers, those receiving pocket money, and those whose fathers and friends use tobacco.

68. Sreedharan S, Kamath MP, Khadilkar U, Hegde MC, Kumar RM, Mudunuri RR, Tripuraneni SC.

Effect of snuff on nasal mucosa.

Am J Otolaryngol. 2005 May-Jun;26(3):151-6.

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Purpose: The inhalation of nasal snuff (powdered tobacco) is a common addiction in the Indian subcontinent. In the western world, there is a resurgence of interest in nasal snuff because it does have the morbidity associated with smoked tobacco. Very few studies have reported the long-term effects of snuff on nasal mucosa. The objective of the present study was to investigate the effect of long-term use of snuff on the nasal mucosa.

Materials and methods: We conducted a retrospective study on 29 snuff users. We investigated the reasons for initiation of this particular form of addiction along with the clinical signs and symptoms of long-term snuff usage. At the time of the study, all patients complained of one or more nasal symptoms. Nasal obstruction and nasal discharge taken together were reported by 62.5% of patients. Gross mucosal edema of the septum and turbinates was the main finding on nasal examination. The absolute eosinophil count and total serum immunoglobulin E were elevated in 62.5% and 66.7% of patients, respectively. On skin prick test, 41% of patients reacted positively to snuff and 25% to tobacco. Histopathologic examination of the turbinates (16 patients) showed squamous metaplasia, capillary proliferation, capillary and venous dilatation, inflammatory cell reaction, subepithelial edema, and fibrosis.

Conclusion: Much has been written about the advantages of nasal snuff over products that deliver tobacco smoke. Our study shows that snuff users, after long-term abuse, develop a form of chronic rhinitis, as a consequence of which they develop blocked and

stuffy noses. We conclude that nasal snuff is not a suitable substitute for smoked tobacco because it does not avoid ill health.

69. Srinath Reddy K, Shah B, Varghese C, Ramadoss A.

Responding to the threat of chronic diseases in India.

Lancet. 2005 Nov 12;366(9498):1744-9

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At the present stage of India's health transition, chronic diseases contribute to an estimated 53% of deaths and 44% of disability-adjusted life-years lost. Cardiovascular diseases and diabetes are highly prevalent in urban areas. Tobacco-related cancers account for a large proportion of all cancers. Tobacco consumption, in diverse smoked and smokeless forms, is common, especially among the poor and rural population segments. Hypertension and dyslipidaemia, although common, are inadequately detected and treated. Demographic and socioeconomic factors are hastening the health transition, with sharp escalation of chronic disease burdens expected over the next 20 years. A national cancer control programme, initiated in 1975, has established 13 registries and increased the capacity for treatment. A comprehensive law for tobacco control was enacted in 2003. An integrated national programme for the prevention and control of cardiovascular diseases and diabetes is under development. There is a need to increase resource allocation, coordinate multisectoral policy interventions, and enhance the engagement of the health system in activities related to chronic disease prevention and control.

70. Sushma C, Sharang C.

Pan masala advertisements are surrogate for tobacco products

Indian J Cancer. 2005 Apr-Jun;42(2):94-8

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Background: Pan masala is a comparatively recent habit in India and is marketed with and without tobacco. Advertisements of tobacco products have been banned in India since 1st May 2004. The advertisements of plain pan masala, which continue in Indian media, have been suspected to be surrogate for tobacco products bearing the same name. The study was carried out to assess whether these advertisements were for the intended product, or for tobacco products with same brand name.

Materials and methods: The programme of a popular television Hindi news channel was watched for a 24-h period. Programmes on the same channel and its English counterpart were watched on different days to assess whether the advertisements were repeated. The total duration of telecast of a popular brand of plain pan masala (Pan

Parag) was multiplied by the rate charged by the channel to provide the cost of advertisement of this product. The total sale value of the company was multiplied by the proportion of usage of plain pan masala out of gutka plus pan masala habit as observed from a different study, to provide the annual sale value of plain pan masala product under reference.

Results: The annual sale value of plain Pan Parag was estimated to be Rs. 67.1 million. The annual cost of the advertisement of the same product on two television channels was estimated at Rs. 244.6 million.

Conclusion: The advertisements of plain pan masala seen on Indian television are a surrogate for the tobacco products bearing the same name.

71. Avasn Maruthit Y, Rao RS, Palivela H, Thakre S.

Impact of gutkha chewing & smoking on microbial environment of oral cavity: a case study on slum dwellers of selected areas in Visakhapatnam.

J Environ Sci Eng. 2004 Oct;46(4):268-73.

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Oral diseases are still a neglected epidemic. During the recent years, in India, both in urban and rural, consumption of tobacco in the form of direct chewing of gutkha is alarmingly increasing especially in the young adults as which is major reason for subsistence of oral cancer. In the present investigation an attempt was made to find out the relationship between gutkha chewing including smoking and oral micro flora in some slum dwellers of Visakhapatnam. The subjects were randomly selected and their health data was collected by distributing questionnaire to control and effected subjects. The oral saliva samples were collected from both gutkha chewers, smokers and from control groups by using saline swabs and inoculated on suitable nutrient media. The results revealed that decrease in salivation and mucous formation in gutkha chewers, which further resulted in reduction in number of oral micro flora. Aspergillus species appeared only in gutkha chewers and smokers. Gutkha chewing and smoking thus, may lead to an increase in the oral pathogens by reducing the normal symbiotic microbial flora.

72. D. N. Sinha, P. C. Gupta

Tobacco use among school personnel in Orissa

Indian J Public Health. 2004 Jul-Sep;48(3):123-7.

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Tobacco use prevalence, knowledge and attitude was assessed among school personnel in Orissa. A single cluster sample design with probability proportional to

the enrolment in grades VIII-X was used. Statistical analysis was done using SUDAAN and the C-sample procedure in Epi-Info. The school response rate was 100%. Over 72% of school personnel participated in the survey, the proportion of men being 84%. Current cigarette smoking, bidi smoking and smokeless tobacco use was reported by 26.8%, 30.1% and 38.8% school personnel respectively. Current daily cigarette smoking, bidi smoking and smokeless tobacco use reported by 18.3%, 16.6% and 24.2% school personnel respectively. Men reported significantly more all kinds of daily tobacco use as compared to women. School tobacco control policy on three scales was reported poor (25-39%). However most of the school personnel felt need for such policies (88-98%). Teaching and training on tobacco was reported low (22.7%-35.9%). Most of the school personnel (87-95%) were supportive on different measures on tobacco control issues. Introduction of comprehensive school policies and enforcement on tobacco use may help to reduce adolescent and school personnel tobacco use.

73. D. N. Sinha, P. C. Gupta

Tobacco use among teachers [corrected] in Uttar Pradesh & Uttaranchal, India

Indian J Public Health. 2004 Jul-Sep;48(3):132-7.

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Information about tobacco use prevalence, knowledge and attitude was assessed among school personnel in Uttar Pradesh. A single cluster sample design with probability proportional to the enrolment in grades 8-10 was used. Statistical analysis was done using SUDAAN and the C-sample procedure in Epi-Info. The school response rate was 100%. School personnel response rate ranged from 72-80%, the proportion of men being 84-92%. Current cigarette smoking and smokeless tobacco use reported by all teachers was 21.9% and 75.6% respectively. The prevalence of daily cigarette smoking was ranged by 12.6-15.1%; bidi and other smoking 4.8-13.4%; smokeless tobacco use 16.3-19.8%. Existing school policy on four measures were reported poor however over 72% school personnel felt need for policy prohibiting tobacco use among students and school personnel. Tobacco prevention instruction by teachers did not fare much better on six different measures (4.9-30.9%). However over 2/3rd school personnel were very supportive on tobacco control issues. There was no training among school personnel on tobacco use prevention skills (3.7%). However most of the school personnel (67.1%) were curious about getting such trainings. A positive environment for tobacco use prevention needs to be created by adopting comprehensive tobacco control policies for schools.

First step towards this may be training of school personnel on tobacco use prevention skill and supply of teaching materials.

74. D. N. Sinha, S. Roychowdhury

Tobacco control practices in 25 schools of West Bengal

Indian J Public Health. 2004 Jul-Sep;48(3):128-31.

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Information about tobacco use prevalence, knowledge and attitude was assessed among school personnel in schools of West Bengal. Statistical analysis was done using SUDAAN and the C-sample procedure in Epi-Info. The school response rate was 100%. Current any smoking and smokeless tobacco use was reported by 30.9% and 13.1% school personnel, respectively. Current daily smoking, and smokeless tobacco use reported by 20.4%, and 5.8% school personnel respectively. Men reported significantly more for all kinds of daily tobacco use as compared to women. School tobacco control policy on three scales was reported poor (17.7-30%). However most of the school personnel felt need for such policies (82.7-93.6%). Teaching and training on tobacco was reported low (29.9%-50.4%). However most of the school personnel (79.1-93.6%) were supportive on different measures of tobacco control. Training of school personnel may provide students with essential tools to help them adopt and maintain a smoke free lifestyle.

75. D. N. Sinha, P. C. Gupta, C. W. Warren, S. Asma

School policy and tobacco use by students in Bihar, India

Indian J Public Health. 2004 Jul-Sep;48(3):118-22.

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The association between school tobacco policies and tobacco use prevalence among students were examined. A two stage cluster sample design with probability proportional to the enrolment in grades VIII-X was used. Comparison was made between schools with a tobacco policy (Federal schools) and schools without a policy (State schools). Stratified probability samples of 50 schools each were selected. SUDAAN and the C-sample procedure in Epi-Info was used for statistical analysis. Students from State schools (without tobacco policy) reported significantly higher ever and current any tobacco use, current smokeless tobacco use and current smoking compared to Federal schools (with tobacco policy) both in rural and urban areas. Classroom teaching on the harmful effects of tobacco was significantly higher (17-24 times) in Federal schools than State schools both in rural and urban areas. Parental tobacco use was similar for students in Federal and State schools. Students attending state schools were more likely than students

attending Federal schools to have friends who smoke or chew tobacco. These findings suggest that the wider introduction of comprehensive school policies may help to reduce adolescent tobacco use.

76. D. N. Sinha, P. C. Gupta, M. Pednekar

Tobacco use among students in Bihar (India)

Indian J Public Health. 2004 Jul-Sep;48(3):111-7.

School of Preventive Oncology, Patna, Bihar, India.

Determination of the prevalence and attitudes toward tobacco use was assessed among 13-15 years school students in Bihar (India). Settings and design: Schools having grade 8-10 in Bihar. A two stage cluster sample design was used. SUDAAN and the C-sample procedure in Epi-Info was used for statistical analysis. Of the 2636 respondents, 71.8% (76.5% boys, 57.2% girls) were ever tobacco users; of them 48.9% had used tobacco before 10 years of age. Current use was reported by 58.9% (Boys 61.4%, Girls 51.2%); smokeless tobacco by 55.6% (Boys 57.6%, Girls 49.2%); and smoking by 19.4% (23.0% boys, 7.8% girls). Nearly one third (29%) students were exposed to ETS inside their homes and nearly half (48%) outside their homes. Almost all students reported watching cigarette and gutka advertisements in almost all kinds of media and events. Tobacco use by parents and friends, knowledge on harmful effects of chewing tobacco, smoking and environmental smoke, and attitudes on tobacco use by others were strongly associated with student tobacco use. Current tobacco use was reported significantly more by students who received pocket money/or were earning than by students who did not receive any pocket money/or did not earn (p value for trend <0.0001). Over half of current users (56%) bought their tobacco products from stores; of these, over 3/4th (77.2%) of them despite their age, had no difficulty in procuring these products. Teaching in schools regarding harmful effects of tobacco use was non-existent (3%). This urgently requires a comprehensive prevention program in schools and the community especially targeted towards girls.

77. N. Sikdar, R. R. Paul, B. Roy

Glutathione S-transferase M3 (A/A) genotype as a risk factor for oral cancer and leukoplakia among Indian tobacco smokers

Int J Cancer. 2004 Mar;109(1):95-101.

Anthropology and Human Genetics Unit, Biological Sciences Division, Indian Statistical Institute, Kolkata, India.

Polymorphism in glutathione S-transferase (GST) genes, causing variations in enzyme activities, may influence susceptibility to oral cancer and leukoplakia in smokers and/or smokeless tobacco users. In this case-control study consisting of 109 leukoplakia and 256 oral cancer patients and 259 controls, genotype frequencies at GSTM1, GSTT1, GSTM3 and GSTP1 loci were determined by polymerase chain reaction-restriction fragment length polymorphism methods and analyzed by multiple logistic regression to determine the risks of the diseases. There were no significant differences in the distributions of GSTM1, GSTM3 and GSTT1 genotypes in patients and controls when all individuals were compared. In contrast, frequencies of ile/ile genotype at codon 105 and variant val-ala haplotype of GSTP1 was significantly higher (OR = 1.5; 95% CI=1.0-2.0) and lower (OR=1.4; 95% CI=1.0-1.9) in oral cancer patients compare to controls, respectively. The impacts of all genotypes on risks of oral cancer and leukoplakia were also analyzed in patients with different tobacco habits and doses. Increased risks of cancer and leukoplakia were observed in tobacco smokers with GSTM3 (A/A) genotype (OR=2.0, 95% CI=1.0-4.0; OR=2.0, 95% CI=1.0-4.4, respectively). So, GSTM3 (A/A) genotype could become one of the markers to know which of the leukoplakia would be transformed into cancer. Heavy tobacco chewing (>124 chewing-year) increased the risk of cancer in individuals with GSTT1 homozygous null genotype (OR=3.0; 95% CI=1.0-9.8). Furthermore, increased lifetime exposure to tobacco smoking (>11.5 pack-year) increased the risk of leukoplakia in individuals with GSTM1 homozygous null genotype (OR=2.4; 95% CI=1.0-5.7). It may be suggested that polymorphisms in GSTP1, GSTM1, GSTM3 and GSTT1 genes regulate risk of cancer and leukoplakia differentially among different tobacco habituals.

78. Gupta PC, Ray CS.

Epidemiology of betel quid usage.

Ann Acad Med Singapore. 2004 Jul;33(4 Suppl):31-6

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Betel quid chewing is an ancient practice common in many countries of Asia and among migrated communities in Africa, Europe and North America. It enjoys complete social acceptance in many societies and is also popular among women. In its most basic form, betel quid consists of betel leaf (*Piper betel*), areca nut, the main psychoactive ingredient, and slaked lime (calcium hydroxide). Areca nut is said to be the fourth most commonly used psychoactive substance in the world, after caffeine, nicotine and alcohol. There are a great variety of ingredients and ways of preparing betel quid in different countries. In some, particularly in India, tobacco is added to the quid. In recent years, commercially-manufactured non-perishable forms of betel quid (pan masala or betel quid

mixtures and gutka), not containing betel leaf, have been marketed. Within a short period of about 2 decades, this industry has risen in value to several hundred US million dollars. Use of areca nut in any form is not safe for oral health; the use of commercially manufactured forms seems even riskier.

79. Gupta PC, Sreevidya S.

Smokeless tobacco use, birth weight, and gestational age: population based, prospective cohort study of 1217 women in Mumbai, India.

BMJ. 2004 Jun 26;328(7455):1538

Epidemiology Research Unit, Tata Memorial Center, Dr Ernest Borges Marg, Parel, Mumbai-400012, India.

Objectives: To study the effect of using smokeless tobacco during pregnancy on babies' birth weight and gestational age at birth.

Design: Population based, prospective cohort study using a house to house approach.

Setting: Eight primary health post areas in the city of Mumbai (Bombay), India.

Participants: 1217 women who were three to seven months pregnant and planning to deliver in the study area. 1167 women (96%) were followed up.

Main outcome measures: Birth weight and gestational age in singleton births.

Results: Smokeless tobacco use was associated with an average reduction of 105 g in birth weight (95% confidence interval 30g -181g) and a reduction in gestational age of 6.2 (3.0 to 9.4) days. The odds ratio for low birth weight was 1.6 (1.1-2.4), adjusted by logistic regression for maternal age, education, socioeconomic status, weight, anaemia, antenatal care, and gestational age. The adjusted odds ratio for preterm delivery (<37 weeks) was 1.4 (1.0-2.1); for delivery before 32 weeks it was 4.9 (2.1-11.8) and before 28 weeks it was 8.0 (2.6 - 27.2).

Conclusion: Consumption of smokeless tobacco during pregnancy decreases gestational age at birth and birth weight independent of gestational age. It should receive specific attention as a part of routine prenatal care.

80. Kulkarni V, Saranath D.

Concurrent hypermethylation of multiple regulatory genes in chewing tobacco associated oral squamous cell carcinomas and adjacent normal tissues.

Oral Oncol. 2004 Feb;40(2):145-53

Department of Molecular Medicine and Biology, Jaslok Hospital and Research Centre, 15 Dr. G. Deshmukh Marg, Mumbai 400 026, India.

The methylation pattern in the promoter region of p16, DAPK, MGMT and GSTP1 genes was investigated in oral cancer tissues and tumor associated adjacent tissues, using

methylation specific PCR assay. The samples constituted 60 primary oral tumors and corresponding adjacent clinically and histopathologically normal mucosa, and buccal epithelial scrapings from 20 normal healthy individuals without any tobacco habits. The incidence of hypermethylation in oral tumor and adjacent mucosa for p16 gene was 66.7 and 50%, for DAPK was 68.3 and 60%, and MGMT gene was 51.7 and 26.7%, respectively. The overall hypermethylation in the three genes in the primary tumor was 86.7%, and corresponding adjacent normal mucosa tissues 76.7%. Hypermethylation was not observed in the promoter region of GSTP1 gene in either the primary tumors or the corresponding adjacent normal mucosa. Absence of aberrant methylation in the four genes was noted in buccal scrapings from normal healthy individuals with no tobacco habits. Thus, a high frequency of promoter region hypermethylation was observed in p16, DAPK and MGMT genes in oral cancer tissues as well as in corresponding adjacent normal mucosa. Our results indicate that epigenetic alteration of these genes is a frequent event in oral cancer, and is an early event observed in normal oral mucosa of the patients, indicating the critical importance of the epigenetic alteration in chewing tobacco associated oral carcinogenesis.

81. Patel MM, Pandya AN.

Relationship of oral cancer with age, sex, site distribution and habits.

Indian J Pathol Microbiol. 2004 Apr;47(2):195-7

Department of Pathology, Government Medical College, Surat, Gujarat, India.

Many studies are carried out regarding age incidence, tobacco smoking and sites of oral cancer, but in Gujarat tobacco chewing in form of Gutkha is more common than smoking and start during preteen years. Tobacco chewing causing chronic inflammation, submucous fibrosis and oral cancer. This study was conducted on 504 patients to find out if there is increasing incidence of oral cancer in lower age group and its relation with sex as well which site was commonly affected. There was statistically significant increase in oral cancer in lower age group, and anatomically anterior part of oral cavity showed involvement in 61.32% of cases. Though males were affected more but female cases were 25%. So tobacco chewing has got detrimental effect on oral cavity.

82. P. S. Patel, M. H. Shah, F. P. Jha, G. N. Raval, R. M. Rawal, M. M. Patel, J. B. Patel, D. D. Patel

Alterations in plasma lipid profile patterns in head and neck cancer and oral precancerous conditions

Indian J Cancer. 2004 Jan-Mar;41(1):25-31.

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Background: The changes in lipid profile have long been associated with cancer because lipids play a key role in maintenance of cell integrity. AIMS: The present study evaluated alterations in plasma lipid profile in untreated head and neck cancer patients as well as patients with oral precancerous conditions (OPC) and its association with habit of tobacco consumption.

Materials and methods: This hospital-based case control study included 184 head and neck cancer patients, 153 patients with OPC and 52 controls. Plasma lipids including: (i) Total cholesterol, (ii) LDL cholesterol (LDLC), (iii) HDL cholesterol (HDLC) (iv) VLDL cholesterol (VLDLC) and (v) triglycerides were analysed by spectrophotometric kits.

Statistical analysis used: Student's t-test was performed to compare mean values of the parameters.

Results: A significant decrease in plasma total cholesterol and HDLC was observed in cancer patients ($P=0.008$ and $P=0.000$ respectively) as well as in patients with OPC ($P=0.014$ and $P=0.000$, respectively) as compared to the controls. The plasma VLDL and triglycerides levels were significantly lower in cancer patients as compared to the patients with OPC ($P=0.04$) and controls ($P=0.059$). The tobacco habituates showed lower plasma lipid levels than the non-habituates. Our data strengthen the evidence of an inverse relationship between plasma lipid levels and head and neck malignancies as well as OPC.

Conclusions: The lower levels of plasma cholesterol and other lipid constituents in patients might be due to their increased utilization by neoplastic cells for new membrane biogenesis. The findings strongly warrant an in-depth study of alterations in plasma lipid profile in head neck cancer patients.

83. R. Sharma, M. S. Pednekar, A. U. Rehman, R. Gupta

Tobacco use among school personnel in Rajasthan, India

Indian J Cancer. 2004 Oct-Dec;41(4):162-6.

Healis, Sekhsaria Institute of Public Health, Navi Mumbai, India.

Background: A very little information about tobacco use among school personnel is available. This is a step to have cross country and within country data using standardized methodology. AIMS: To obtain baseline information about tobacco use prevalence, knowledge and attitude among school personnel.

Study design: Two stage cluster sample.

Setting: A state of Rajasthan.

Materials and methods: A cross-sectional study, using anonymous self-administered questionnaire. A sample of schools with probability proportional to the enrollment in grades 8-10. All school personnel in sampled schools were eligible to participate.

Statistical analysis: Percentage, 95% confidence interval.

Results: School response rate was 97.4% (75/77) and school personnel response rate was 67.2% (909/1352). Majority of school personnel (men 69%, women 31%) were school teachers (78.3%). The prevalence of ever any tobacco use was reported by 35.9%, more among men than women (46.2% vs. 13.0%). The prevalence of current daily smoking was reported by 14.4% (men 20.6%, women 0.8%) and occasional by 7.3%, where as current daily smokeless tobacco use was 11.7% (men 16.4%, women 1.1%) and occasional 13.6%. Current daily tobacco use was significantly more among men than women. Four out of nine reported their schools have a tobacco prohibiting policy for both students (48.4%) as well as for school personnel (44.4%) and about same (47.2%) reported their schools enforce its tobacco policy or rule. Over 85% of all school personnel strongly support the tobacco control policies and wanted training in tobacco cessation and prevention.

Conclusions: First study from Rajasthan to report tobacco use among school personnel. School personnel not only strongly support the tobacco control policies but also ready to work for its successful implementation with proper training.

84. Rai R, Kulkarni V, Saranath D.

Genome wide instability scanning in chewing-tobacco associated oral cancer using inter simple sequence repeat PCR.

Oral Oncol. 2004 Nov;40(10):1033-9

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Genomic instability plays a major role in cancer, facilitating tumour progression and tumour heterogeneity. Inter simple sequence repeat PCR (ISSR-PCR) is a sensitive tool for detection of whole genome scanning. In fifteen oral cancer patients, using tumor tissue and adjacent normal tissue DNA, we investigated genomic instability regions using ISSR-PCR assay. The genomic fragments were cloned, sequenced and identified. Two-anchored dinucleotide repeat primers, (CA)(8)A/GG and (CA)(8)A/GC/T, were used in the study. About 40-50 fragments were observed on polyacrylamide gel electrophoresis, with 25 distinct fragments of less than 2 kb. The electrophoretic pattern highlighted several distinct fragments in tumor adjacent normal tissues. The distinct fragments of 258, 325, 430, 440, 600 and 900 bp sizes using (CA)(8)A/GG primer, and 300, 475, 675 and 800 bp using (CA)(8)A/GC/T primers, in the normal tissues showed partial (>50%) or complete loss in multiple tumor tissues. These fragments were eluted from the gel, cloned in pMos Blue vector and subjected to nucleotide sequencing. Insilico analysis defined the specific genomic sequences, given as follows: RP11-399D2 () on chromosome (chr)4; RP1-39J2 (), NKp44RG () and RP11-518I13 () on chr6; NC-T-2 ()

on chr7; RP11-586K2 () and RP11-495O10 () on chr8; RP11-101K10 () on chr9; R-794A8 () on chr14; and RP11-679B19 () on chr16. The sequences of our clones have been submitted to NCBI gene bank, accession numbers to, and the Genomic Instability Index was calculated and ranged from 6% to 28.5% (median 12%) in the oral cancer samples, excluding one case where genomic instability was not observed. Thus, our results indicate presence of widespread genomic alterations in chewing-tobacco associated oral cancers.

85. Rai R, Mahale A, Saranath D.

Molecular cloning, isolation and characterisation of ERK3 gene from chewing-tobacco induced oral squamous cell carcinoma.

Oral Oncol. 2004 Aug;40(7):705-12

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The mitogen activated serine/threonine kinases (MAPKs) constitute extracellular signal-regulated protein kinases (ERKs), c-Jun N-terminal kinases (JNKs) and p38 MAPK, with an important role in cell proliferation and transformation. Earlier studies from our laboratory had indicated a role for MAPK pathway in oral cancer. Our current study was aimed at examining the role of a MAPK-ERK3, in chewing-tobacco associated oral squamous cell carcinoma. We constructed a cDNA library from primary oral cancer tissue, cloned and isolated the ERK3 gene. The gene was sequenced and the sequence submitted to GenBank (Accession number AF420474). The oral cancer ERK3 clone demonstrated 100% homology to human ERK3 isolated from fetal skeletal muscle, with four specific nucleotide alterations in the non-coding region of the gene, comprising deletion of 'TTT' between 2701 and 2705 nt; 'G' to 'T' substitution at 188 nt; insertion of 'A' between 121 and 122 nt, and insertion of 'CTTTA' between 3391 and 3392 nt. Southern analysis of EcoRI genomic digests indicated ERK3 specific fragments of 11, 8.6, 6.5 and 3.2 kb sizes. The mRNA transcript analysis defined a single transcript of 4.5 kb. RT-PCR analysis revealed a three- to eight-fold increase in ERK3 expression in a majority (90%) of oral cancer tissues and peripheral blood cells (61.5%) of the patients, whereas absence or low levels of expression was observed in peripheral blood cells of 74% clinically normal healthy individuals with no tobacco habits, and overexpression in PBC from 26% normal individuals. The alterations in the non-coding region of ERK3 gene cloned from oral cancer tissue, may affect stability or regulation of mRNA, resulting in overexpression in the patient samples. The overexpression of the gene in the normal healthy individuals may be indicative of increased risk of developing oral cancers in this group.

86. Ranganathan K, Devi MU, Joshua E, Kirankumar K, Saraswathi TR.

Oral submucous fibrosis: a case-control study in Chennai, South India.

J Oral Pathol Med. 2004 May;33(5):274-7

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Background: Oral submucous fibrosis (OSF) is a pre-cancerous condition caused by the use of areca nut in various forms. There are very few published reports on areca nut use and OSF from Chennai, South India.

Methods: A hospital-based case-control study on habits and OSF was performed in Chennai over a 3-year period. A total of 185 consecutive patients with OSF were matched with age- and sex-matched controls. History was recorded in a pre-determined format by qualified dental surgeons.

Results: The male to female ratio of OSF cases was 9.9 : 1. All areca nut products were associated with OSF, with the risk being greatest for pan masala. The duration of the habit was more significant than the frequency of the chewing habit.

Conclusion: The present study confirms the strong association between areca nut use and OSF and the increasing use of pan masala.

87. S. Jhavar, R. Sarin, R. Mulherkar, A. Benner, J. P. Agarwal, K. Dinshaw

Glutathione S-transferase M1 or T1 null genotype as a risk factor for developing multiple primary neoplasms in the upper aero-digestive tract, in Indian males using tobacco

Oral Oncol. 2004 Jan;40(1):84-91.

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In this study conducted amongst Indian male tobacco users with upper aero-digestive tract (UADT) squamous carcinoma, 30 patients with multiple primary neoplasms (MPN) were compared with 28 age and sex matched patients with a single primary neoplasm (SPN) for various environmental factors (form of tobacco use, alcohol, radiotherapy for index cancer) and genetic parameters (family history of UADT cancers and GSTT1/GSTM1 genotype). The GSTM1/T1 null genotype, seen in 60% patients with MPN versus 33% patients with SPN (P=0.03) had an odds ratio of 3.7 [CI=1.14-11.99; P=0.03] for developing MPN. Tobacco use in the form of smoking with or without chewing, as opposed to only chewing, and regular alcohol intake were the two other factors with almost three fold increased risk for the development of MPN, although, the effect was not statistically significant. All three patients with a family history of UADT cancer developed MPN, suggesting an inherited predisposition.

88. Sunny L, Yeole BB, Hakama M, Shiri R, Sastry PS, Mathews S, Advani SH.

Oral cancers in Mumbai, India: a fifteen years perspective with respect to incidence trend and cumulative risk.

Asian Pac J Cancer Prev. 2004 Jul-Sep;5(3):294-300.

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Objective: We estimated the time trends in the incidence and the risk of developing an oral cancer in Mumbai, Indian population using the data collected by the Bombay Population Based Cancer Registry during the 15-year period from 1986 to 2000.

Methods: A total of 9,670 oral cancers (8.2% of all neoplasms) were registered, of which 6577 were in males and 3093 in females (10.7% and 5.4% of the respective totals for the two genders). For evaluation of the trend, we applied a linear regression model based on the logarithm of the observed incidence rates. The annual percentage changes were also computed for the incidence rates to evaluate the time trend.

Results: In males, a statistically significant decreasing trend in the overall age-adjusted incidence rates were observed during the period 1986 to 2000, with an yearly decrease of 1.70%. This decrease was significant for men above the age of 40, but for young adult men below the age of 40, there was no significant decrease, the level being stable. In females, the overall decreasing trend in the age-adjusted incidence rates of oral cancers was not significant, but in the age group 40-59, a significant decline was observed. The probability estimates indicated that one out of every 57 men and one out of every 95 women will contract any oral cancer at some time in their whole life and 97% of the chance is after he or she completes the age of 40.

Conclusion: The observed decreasing trend in oral cancers in Indian men may be attributed to a decrease in the usage of pan and tobacco. The high prevalence of the usage of smokeless tobacco among young adult men and women may explain the stable trend in oral cancer incidence in this group. These findings help to strengthen the association between tobacco use and oral cancer risk.

89. Bathi RJ, Prabhat

p53 aberrations in oral sub mucous fibrosis and oral cancer detected by immunohistochemistry.

Indian J Dent Res. 2003 Oct-Dec;14(4):214-9.

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Study of expression of p53 oncoprotein in several precancerous and cancer have been done, but only one literature is available regarding p53 expression in Oral Sub Mucous Fibrosis (OMSF), hence this study was taken up (i) to determine the expression of

aberrant p53 in Oral Sub Mucous Fibrosis (OSMF) and Oral Squamous cell carcinoma (SCC) patients. (ii) To study correlation if any between p53 expression and degree of dysplasia in OSMF and SCC patients and (iii) To study correlation if any between p53 expression and habits in OSMF and SCC patients. Study Design consists of biopsy specimens of 38 cases of OSMF and 37 cases of Squamous cell carcinoma were subjected for staining by immunohistochemistry for p53 protein using LSAB visualization system kit. Clinical details along with habits were recorded and the data analyzed with t-test and chi-square test. Results of the study reveals 18 cases of OSMF and 26 cases of SCC were positive for p53 protein. Only 4 cases of SCC showed (++) grade and the rest all had (+) grade. Out of 75 patients, 65 had the habit of smoking and chewing, 4 patients history of habit was not known. Among patients with habits (65), 40 specimens were +ve for p53 stain and 2 out of 6 without history of habit, 2 out of 4 unknown history of habit took up p53 stain. To conclude study showed higher percentage of p53 positive cells in oral cancer cases when compared to oral sub mucous fibrosis cases. It suggests p53 expression may correlate with increase in dysplasia or malignant transformation. Both smoking and chewing habits had a significant role in p53 positive expression.

90. G. Thomas, M. Hashibe, B. J. Jacob, K. Ramadas, B. Mathew, R. Sankaranarayanan, Z. F. Zhang

Risk factors for multiple oral premalignant lesions

Int J Cancer. 2003 Nov 1;107(2):285-91.

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Oral leukoplakia, oral submucous fibrosis and erythroplakia are 3 major types of oral premalignant lesions. Multiple oral premalignant lesions may possibly develop due to field cancerization, where carcinogenic exposures can cause simultaneous genetic defects to the upper aerodigestive tract epithelium, putting the epithelium at high risk for development of premalignant lesions at different stages of carcinogenesis. There have been no epidemiological studies on risk or protective factors of the disease. A case-control study was conducted with data from the baseline screening of a randomized oral cancer screening trial in Kerala, India. A total of 115 subjects with multiple oral premalignant lesions (8-10% of oral premalignant lesions in our case series) were included: 64 subjects with oral leukoplakia and oral submucous fibrosis, 19 subjects with oral leukoplakia and erythroplakia, 22 subjects with oral submucous fibrosis and erythroplakia and 10 subjects with all 3 lesions. Individuals without oral lesions were considered controls (n=47,773). The odds ratio (OR) for ever tobacco chewers was 37.8 (95% confidence interval (CI)=16.2-88.1) when adjusted for age, sex, education, BMI, smoking, drinking and fruit/vegetable intake. Dose-response relationships were seen for the frequency ($p < 0.0001$) and duration of tobacco chewing ($p < 0.0001$) with the risk of multiple oral premalignant lesions. Whereas alcohol drinking may

possibly be a risk factor for multiple oral premalignant lesions, smoking was not associated with the risk of multiple oral premalignant lesions (OR=0.9, 95%CI=0.5-1.7). The results suggest that tobacco chewing was the most important risk factor for multiple oral premalignant lesions and may be a major source of field cancerization on the oral epithelium in the Indian population.

91. Gupta PC, Ray CS.

Smokeless tobacco and health in India and South Asia.

Respirology. 2003 Dec;8(4):419-31

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South Asia is a major producer and net exporter of tobacco. Over one-third of tobacco consumed regionally is smokeless. Traditional forms like betel quid, tobacco with lime and tobacco tooth powder are commonly used and the use of new products is increasing, not only among men but also among children, teenagers, women of reproductive age, medical and dental students and in the South Asian diaspora. Smokeless tobacco users studied prospectively in India had age-adjusted relative risks for premature mortality of 1.2-1.96 (men) and 1.3 (women). Current male chewers of betel quid with tobacco in case-control studies in India had relative risks of oral cancer varying between 1.8-5.8 and relative risks for oesophageal cancer of 2.1-3.2. Oral submucous fibrosis is increasing due to the use of processed areca nut products, many containing tobacco. Pregnant women in India who used smokeless tobacco have a threefold increased risk of stillbirth and a two- to threefold increased risk of having a low birthweight infant. In recent years, several states in India have banned the sale, manufacture and storage of gutka, a smokeless tobacco product containing areca nut. In May 2003 in India, the Tobacco Products Bill 2001 was enacted to regulate the promotion and sale of all tobacco products. In two large-scale educational interventions in India, sizable proportions of tobacco users quit during 5-10 years of follow-up and incidence rates of oral leukoplakia measured in one study fell in the intervention cohort. Tobacco education must be imparted through schools, existing government health programmes and hospital outreach programmes.

92. Kaur J, Ralhan R.

Establishment and characterization of a cell line from smokeless tobacco associated oral squamous cell carcinoma.

Oral Oncol. 2003 Dec;39(8):806-20

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A cell line, AMOS-III has been established from the surgically resected specimen of an untreated primary human oral squamous cell carcinoma of the floor of mouth from a chronic smokeless tobacco consumer. Immunocytochemical analysis showed epithelial specific antigen, cytokeratins 5, 10, 13 and 16 and integrin alpha(6) markers in AMOS-III cells, confirming the epithelial lineage of the cell line. Analyses of morphology, ultrastructure, karyotype, anchorage independent growth and immunocytochemical properties of the cell line demonstrated the transformed phenotype of epithelial cells. AMOS-III cells have doubling time of 42-44 h. Giemsa-banding patterns of chromosomes confirmed the human origin of the AMOS-III cells. Molecular analysis of cancer-related gene products, p53 and p21(cip1/waf1) showed the presence of wild type p21(cip1/waf1) and truncated p53 proteins. The molecular mechanism underlying the action of retinoids in preventing the occurrence of second primary tumors in oral cancer patients remain to be clearly defined. Treatment of AMOS-III cells with all-trans retinoic acid (ATRA) at 10(-4) microM resulted in 81% cell death. ATRA treatment resulted in enhanced expression of p21(cip1/waf1), nuclear translocation of retinoic acid receptors and apoptotic cell death. Thus, this cell line provides an in vitro model for elucidating the mechanism involving p53 inactivation and p21(cip1/waf1) overexpression in smokeless tobacco-induced oral cancer. Furthermore, the ATRA responsiveness of the cell line underscores its potential utility in identifying the retinoid responsive molecular targets in oral cancer cells.

93. Mehrotra R, Singh M, Kumar D, Pandey AN, Gupta RK, Sinha US.

Age specific incidence rate and pathological spectrum of oral cancer in Allahabad.

Indian J Med Sci. 2003 Sep;57(9):400-4.

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Background: Cancer of the oral cavity is one of the commonest cancers in India. Use of smokeless tobacco (Pan masala, Zarda etc) is on the increase in North India and specially in Uttar Pradesh. **AIMS:** To assess the patients characteristics and histopathological subtypes of the oral cancer in our region.

Setting and design: A single institutional retrospective study of 11 years from 1990 to 2000 was designed. Data was collected year wise using the tumour registry data. **MATERIAL AND METHODS:** A total of 40,559 biopsies were examined in the department during 1990-2000, out of which the oral cavity constituted 759 biopsies. The data was analysed with emphasis on age, sex, risk factors, site and histology.

Statistical analysis: The data was analysed utilizing the Kolomogroo-Smirnov two sample test.

Results: A comparison of the age specific incidence rates of oral cancer during 1990-2000 in Allahabad showed that the incidence was maximum in the 50-59 years age group and squamous cell carcinoma grade I was the most prevalent type. Of the total of 759 biopsies from oral cavity, 303 malignant cases. 232 (76.57%) were males and 71 (23.43% were females with a male to female ratio of 3.27:1. The tongue was the most frequently involved site--found in 42.57% cases. On an average, 63 new cases of oral cavity per annum were detected during this period.

Conclusion: Properly structured site specific data like this can augment National Cancer Registry Programme (NCRP) and is an essential indicator for the magnitude and the pattern of the cancer problem in India Urgent public health measures like public education and oral cancer awareness are required to curb this avoidable epidemic.

94. Mishra R, Das BR.

Early overexpression of Cdk4 and possible role of KRF and c-myc in chewing tobacco mediated oral cancer development.

Mol Biol Rep. 2003 Dec;30(4):207-13

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Cyclin Dependent Kinase 4 (Cdk4) is known to be an oncogene and is involved in various cancers. It is over-expressed either by genomic amplification or by c-myc dependent manner. Our preliminary results indicate high expression of protein and mRNA as well as absence of genomic amplification in early oral cancer development. One transcription factor (TF) binding site has been detected from -281 to -298 by using DNase I foot printing and confirmed by electrophoretic mobility shift assay. This is a novel DNA sequence. The recruitment of this new TF as well as the earlier reported c-myc was analyzed in various stage of oral cancer development. The binding activity of the new TF is present in normal tissues and observed more in initial stage samples whereas c-myc expression was absent in normal and more in higher stage of oral cancer development. On the basis of these findings we propose the new TF to be a possible Cdk4 Regulating Factor (KRF). This might maintain the basal level transcription in normal and activates Cdk4 transcription in the initial stage, where as the same role is carried by c-myc in higher stage of chewing tobacco mediated oral cancer development.

95. Sawant SS, Naresh KN, D'Cruz A, Ogale SB, Vaidya MM.

Demonstration of cytokeratin-5 non-expression in tobacco related oral carcinogenesis--use of reverse transcriptase polymerase chain reaction as a sensitive assay.

Oral Oncol. 2003 Dec;39(8):789-95

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Cytokeratins (CK) are the epithelia specific intermediate filament proteins. We have shown consistent non-expression of CK-5 protein in human oral pre-cancer and cancer, in earlier studies. To investigate whether non-expression of CK-5 protein is the result of transcriptional or translational block and to evaluate the possibility if CK-5 non-expression can be used as a marker for early diagnosis of tobacco related oral cancer, RT-PCR using CK-5 specific primers was conducted. Out of 36 precancerous lesions and 29 squamous cell carcinomas (SCC) of buccal mucosa (BM) samples studied, 11 and 13 samples respectively of precancer and SCC did not show CK-5 product in RT-PCR. Down regulation of CK-5 mRNA expression was also observed in some samples. Thus, in conclusion, our results have shown that CK-5 non-expression is the result of transcriptional block. We proposed CK-5 non-expression as a potential marker for the early diagnosis of tobacco related oral cancer.

96. Sikdar N, Paul RR, Panda CK, Banerjee SK, Roy B.

Loss of heterozygosity at APC and MCC genes of oral cancer and leukoplakia tissues from Indian tobacco chewers.

J Oral Pathol Med. 2003 Sep;32(8):450-4

Anthropology and Human Genetics Unit, Biological Sciences Division, Indian Statistical Institute, 203 B. T. Road, Kolkata 700 08, India.

Background: Loss of heterozygosity (LOH) at tumor suppressor genes, such as adenomatous polyposis coli (APC) and mutated in colon cancer (MCC) genes, is one of the early events in carcinogenesis of oral tissue in Caucasian and Chinese patients. We wanted to check whether it is also true in Indian oral pre-cancer and cancer patients.

Methods: Loss of heterozygosity at APC and MCC genes was investigated in 57 and 40 unrelated primary oral leukoplakia (a pre-cancerous lesion) and squamous cell carcinomas (SCC), respectively, by polymerase chain reaction.

Results: In these samples, most of the leukoplakia patients had tobacco smoking habit whereas majority of cancer patients had tobacco chewing habit. LOH at APC gene was observed in 4 of 16 (25%) and 1 of 29 (3%) informative tumor and leukoplakia DNAs from tobacco chewers, respectively. LOH at MCC gene was not detected either in tumor or in leukoplakia DNAs.

Conclusion: This infrequent LOH at APC gene of pre-cancer and cancer tissues suggests that it may not be an early event in oral carcinogenesis in these patients.

97. T. R. Sarswathi, S. N. Kumar, K. M. Kavitha

Oral melanin pigmentation in smoked and smokeless tobacco users in India. Clinico-pathological study

Indian J Dent Res. 2003 Apr-Jun;14(2):101-6.

Department of Oral Pathology, Ragas Dental College, Chennai, India.

Tobacco used as smoked and smokeless form induces oral mucosal changes in which intra-oral mucosal pigmentation is one of the clinical manifestations. The melanocyte activity responsible for pigment changes is not well documented in the literature. The present study is undertaken to observe clinical and histological changes in oral buccal and labial mucosa of 41 tobacco users and compared with 8 controls. 95.24% of smokers showed pigmentation of both labial and buccal mucosa. Labial mucosa showed a high degree of pigmentation (81%) than the buccal mucosa (33.3%). 93.3% of alcoholics showed a high degree of pigmentation. Hypermelanocytosis and melanosis were observed in smokers. Pigmentation at the site of quid placement was absent in smokeless tobacco users but mild pigmentation was observed away from the site of quid placement with the concurrent increase in the number of melanocytes and melanocytic activity.

98. V. Gajalakshmi, R. J. Hung, A. Mathew, C. Varghese, P. Brennan, P. Boffetta

Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in southern India

Int J Cancer. 2003 Nov 10;107(3):441-7.

Epidemiological Research Center, Chennai, India.

In India, lung cancer is one of the most common and lethal cancers, and tobacco smoking remains its most important etiologic factors. The objective of our study is to examine the effects of different tobacco consumption forms, including smoking and chewing, on lung cancer risk of men in southern India, especially to compare the effects of bidi smoking to cigarette smoking on lung carcinogenesis. We also evaluated the possible role of Indian alcohol beverages and non-Indian alcohol beverages on lung carcinogenesis. We conducted a case-control study in Chennai and Trivandrum. In total, 778 lung cancer cases and 3,430 controls, including 1,503 cancer controls and 1,927 healthy controls, were recruited. The effects of cigarette, bidi smoking, chewing and alcohol drinking on the risk of lung cancer were estimated from unconditional multivariate logistic regression. We also applied the generalized additive model (GAM) with locally-weighted running-line smoothers (loess) to find the most plausible curve for the dose-response relationship. The results from GAM suggest a plateau after 35 years of smoking or 10 cigarette-equivalent pack-years for both cigarette and bidi. The OR is 4.54 (95%CI=2.96-6.95) and 6.45 (95%CI=4.38-9.50) for more than 30 years of cigarette-only and

bidi-only smoking, respectively, and 6.87 (95%CI=4.62-10.2) and 10.7 (95%CI=5.82-19.6) for more than 12 weighted cumulative cigarette-only and bidi-only consumption, respectively. The lung cancer risk of former cigarette smokers drops down more quickly after quitting smoking compared to former bidi smokers. There is no evidence for the effect of chewing and lung cancer risk nor clear evidence of an effect of overall alcohol drinking among never-smokers, although Indian alcohol drinking seemed to remain associated with lung cancer risk under limited power (OR=2.67, 95%CI=1.02-7.02). Bidi smoking seems to have a stronger carcinogenic effect than cigarette smoking; this difference holds no matter which aspect of smoking was considered.

99. Nagpal JK, Mishra R, Das BR.

Activation of Stat-3 as one of the early events in tobacco chewing-mediated oral carcinogenesis.

Cancer. 2002 May 1;94(9):2393-400

Molecular Oncology and Medical Biotechnology Division, Institute of Life Sciences, Chandrasekharpur, Bhubaneswar, India.

Background: The Jak/Stat signaling pathway transmits signals from many cytokines and growth factor receptors to target genes in the nucleus. Constitutive activation of Stat-3 recently has been observed in many tumor cells, and dysregulation of the Stat signaling pathway has been proposed to be implicated in malignant transformation. In the current study for the first time to the authors's knowledge, the expression of STAT-3 was analyzed in various stages and sites of squamous cell carcinoma of the head and neck (HNSCC).

Methods: Tissue samples from 90 patients of tobacco chewing-mediated HNSCC representing various stages, sites, and differentiation states were selected for studying STAT-3 protein and RNA expression. In vivo localization of STAT-3 was studied by immunohistochemistry of paraffin embedded sections. The presence of STAT-3 and its phosphorylated and activated form pSTAT-3 was checked by Western blotting. mRNA expression was analyzed by reverse transcriptase-polymerase chain reaction (RT-PCR). Apoptosis analysis was conducted by in situ ENA nick end labeling assay and hematoxylin and eosin staining.

Results: Overall, 58.9% of HNSCC tumors showed very high Stat-3 protein accumulation, and 23.3% showed intermediate accumulation whereas 17.8% of HNSCC tumors were negative for Stat-3. No Stat-3 was detected in normal samples, and only one of eight premalignant lesions showed intermediate Stat-3 accumulation. On immunoblotting, very high protein accumulation was detected in T1 and T2 classification, moderate in T3 and T4 ($P = 0.033$, chi-square test), whereas no Stat-3 was detected in normal samples. Similar trend also was found in Stat-3 mRNA expression by RT-PCR

analysis which was high in T1 and T2 (early stages), moderate in T3 and T4 (late stages), and no expression in normal samples. The mean apoptotic indices were 1.75, 1.88, and 1.66 for normal, premalignant lesions, and HNSCC cases, respectively.

Conclusion: Stat-3 activation is an early event in head and neck carcinogenesis though its role in blocking the apoptosis in vivo in solid tumors was not observed.

100. Pande P, Soni S, Kaur J, Agarwal S, Mathur M, Shukla NK, Ralhan R.

Prognostic factors in betel and tobacco related oral cancer.
Oral Oncol. 2002 Jul;38(5):491-9

Department of Biochemistry, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029, India.

Paucity of well-defined prognostic molecular markers severely hampers prediction of the clinical course of squamous cell carcinoma (SCC) of oral cavity. The aim of the study was to evaluate the prognostic significance of impairments in the expression of proteins involved in cell cycle regulation and locoregional spread in oral SCC of habitual betel and tobacco chewers. A prospective study was performed in 105 betel and tobacco consumers with oral SCCs during the period 1988-1999, to evaluate the prognostic relevance of impairments in the expression of proteins involved in cell cycle regulation and locoregional spread. Alterations in the expression of p53, pRb, p16, MDM2, p21, and Ets-1 proteins were determined by immunohistochemical analysis in formalin fixed, paraffin embedded tissue sections from oral SCCs. Analysis of multiple molecular biological factors showed overexpression of p53 in 69/105 (66%) cases, MDM2 in 72/105 (69%) cases, p21 in 57/105 (54%) cases and Ets-1 in 64/105 (61%) cases. Loss of pRb was observed in 58/105 (55%) cases and p16 loss was observed in 72/105 (69%) cases. Interestingly, multivariate analysis revealed loss of pRb as the most significant predictor of advanced tumour stage [P=0.001; Odd's Ratio (OR)=3.5] and overexpression of Ets-1 protein was an independent risk factor for lymph node metastasis (OR: 10.1; P<10⁻⁶). Multiple logistic regression models showed that pRb loss [Hazard's Ratio (HR): 3.93] and p53 overexpression (HR: 2.97) may serve as adverse prognosticators for disease free survival of the patients. The data demonstrate multiple impairments in p53/MDM2/p21/Ets-1 and p16/pRb pathways in betel and tobacco related oral tumourigenesis

101. Teni T, Pawar S, Sanghvi V, Saranath D.

Expression of bcl-2 and bax in chewing tobacco-induced oral cancers and oral lesions from India.

Pathol Oncol Res. 2002;8(2):109-14

Laboratory of Cancer Tenes, Cancer Research Institute, Tata Memorial Centre, Parel, Mumbai, India.

Deregulation of oncogenes and tumor suppressor genes involved in apoptosis has been associated with tumor development and progression. To investigate the involvement of apoptosis regulating proteins in oral cancer in Indian patients, primarily associated with chewing tobacco habits, immunohistochemical expression of bcl-2 and bax was examined in 63 oral squamous cell carcinomas, and 31 putative premalignant lesions. Our studies revealed overexpression of tumor specific cytoplasmic bcl-2 in 56% and bax in 43% oral cancers. The oral cancers in the Indian patients are preceded by premalignant oral lesions; hence oral lesions were examined for bcl-2 and bax expression. We observed aberrant expression of bcl-2 in 16% oral lesions comprising leukoplakias and SMF and bax in 55% oral lesions. We have already reported, p53 expression in these oral cancers and lesions. It was noteworthy that 30% oral cancers demonstrated a p53+bcl2+ pattern, and 14% samples exhibited p53+bcl2+bax+ pattern. However, none of the oral lesions showed concurrent deregulation of p53 and bcl-2 or all the three genes. Interestingly 45% oral lesions were p53-bax+ as compared to 18% oral cancers; while 39% oral lesions were bcl2-bax+ as compared to 14% oral cancers, indicating overexpression of bax in oral lesions, in the absence of p53 and bcl-2 proteins. Significant correlation was observed between positive nodal status and bcl2+ ($p=0.047$) and p53+bcl-2+ ($p=0.01$) in oral cancers. Kaplan Meier survival analysis showed significantly ($p=0.059$) higher survival in patients with p53- oral tumors than with p53+ tumors. Our studies thus indicate frequent overexpression of apoptosis regulators bcl-2, bax and p53 proteins in oral cancers, and a subset of oral lesions, representing early events in oral carcinogenesis. The aberrant bcl-2 expression and loss of p53 function observed, may play an important role in the tumorigenesis of oral cancers by allowing escape from apoptosis and enabling additional genetic alterations to accrue.

102. Mahimkar MB, Buch SC, Samant TA, Kapoor MD, Bhisey RA.

Influence of smokeless tobacco exposure on detoxification status and chromosomal damage in male and female habitues.

Mutat Res. 2001 Apr 5;491(1-2):11-7

Carcinogenesis Division, Cancer Research Institute, Tata Memorial Centre, Parel, 400012, Mumbai, India.

In India, a large number of tobacco chewers and masheri users are chronically exposed to tobacco genotoxicants. Detoxification processes involving cellular glutathione (GSH) and glutathione S-transferases (GST) determine the outcome of exposure to environmental mutagens including those present in tobacco. Hence, in this study, GSH levels, GST activity, GSTM1 genotype and cytogenetic damage were determined using lymphocytes from 114 smokeless tobacco habitues and controls. The study groups comprised of male tobacco chewers, female masheri users, and age- and sex-matched

controls. Irrespective of the tobacco habit, GSH levels and GST activity were higher in females than in males. In both the groups of habitues, GSH levels were similar to those in controls, while a significant reduction in GST activity was observed in tobacco chewers only. The frequency of cytogenetic alterations was significantly elevated in both the groups of habitues with respect to controls. However, break-type aberrations were more frequent in tobacco chewers while gaps were commonly observed in masher users. Differences in the nature of chromosomal alterations in the two groups of habitues appeared to be related to variation in total tobacco exposure and gender-related differences in the efficacy of the GSH/GST detoxification system.

103. Phukan RK, Ali MS, Chetia CK, Mahanta J.

Betel nut and tobacco chewing; potential risk factors of cancer of oesophagus in Assam, India.

Br J Cancer. 2001 Sep 1;85(5):661-7

Regional Medical Research Centre, Indian Council of Medical Research, North East Region, Assam, Dibrugarh, India.

Cancer of the oesophagus is the most commonly diagnosed cancer in males in Assam, in north-eastern India, and ranks second for females. The chewing of betel nut, with or without tobacco and prepared in various ways, is a common practice in the region and a case-control study has been designed to study the pattern of risk associated with different ways of preparing and chewing the nuts. 358 newly diagnosed male patients and 144 female have been interviewed together with 2 control subjects for each case chosen at random from among the attendants who accompanied patients to hospital. There were significant trends in risk ratios associated with the frequency of chewing each day, with the duration of chewing in years and with the age at which the habit was started that were apparent for both males and females and which remained significant after allowance was made for other known risk factors, notably tobacco smoking and alcohol consumption. The adjusted ratios, in comparison with non-chewers, were 13.3 M and 5.7 F for chewing more than 20 times a day, 10.6 M and 7.2 F for persons who had chewed for more than 20 years and 10.3 M and 5.3 F for those who had started before the age of 20. Among the different combinations of ingredients that were chewed the adjusted odds ratios were highest for those who had been using fermented betel nut with any form of tobacco (7.1 M and 3.6 F). The risk associated with tobacco smoking and alcohol consumption, which are high in some parts of the world, were less in Assam than those associated with the chewing of betel nut.

104. Mahale A, Saranath D.

Microsatellite alterations on chromosome 9 in chewing tobacco-induced oral squamous cell carcinomas from India.

Oral Oncol. 2000 Mar;36(2):199-206

Laboratory of Cancer Genes, Cancer Research Institute, Tata Memorial Centre, Parel, Mumbai, India.

Genomic instability as reflected by microsatellite alterations in specific target regions is an important characteristic of oral squamous cell carcinoma (OSCC). Microsatellite instability (MSI) and loss of heterozygosity (LOH) on chromosome 9 has been reported as an early event in oral cancers, primarily from patients in the USA and UK. Hence, we examined 77 primary oral cancer tissues and corresponding peripheral blood cell (PBC) DNA from Indian oral cancer patients for LOH and MSI, using a panel of 11 microsatellite markers spanning chromosome 9 on p and q arms. The patients were long-time (minimum 10 years) tobacco chewers. The matched DNA samples were amplified by polymerase chain reaction, resolved on a denaturing polyacrylamide gel and visualized by silver staining. An overall of 62% (48/77 cases) of the patients demonstrated microsatellite alterations including 27% MSI and 52% LOH, although at individual loci MSI was observed in 3-8% patients and LOH in the informative cases ranged from 4 to 41%. A majority of the alterations occurred on the p arm at 9p21-23, with 85% (41/48 cases) genetic alterations concentrated between markers D9S157 and D9S161. Multiple alterations were seen in 56% (27/48) of the affected cases with 17 patients showing microsatellite alterations in three to eight loci. Our data show the incidence of genetic alterations primarily in the chromosomal region 9p21-23, and may be indicative of involvement of p16 (CDKN2) tumor suppressor gene on chromosome 9p21, in a subset of chewing tobacco-induced oral cancers.

105. Sharma AK, Gupta R, Gupta HP, Singh AK

Haemodynamic effects of pan masala in healthy volunteers.

J Assoc Physicians India. 2000 Apr;48(4):400-1.

Department of Nephrology, Monilek Hospital and Research Center, Jawahar Nagar, Jaipur-302 004.

Objectives: We studied acute haemodynamic effects of pan masala (powdered mixture of areca nut, slaked lime, catechu, and condiments) in healthy volunteers.

Methods: Fifty one males (mean age 28.6 ± 10 years) were evaluated. One pouch (4 g) of pan masala without tobacco was given to each subject under fasting state and effects on pulse and blood pressure (BP) recorded.

Results: At baseline the pulse rate was 75.1 ± 9.0 per minute, systolic BP was 119.1 ± 10.8 mm Hg, and diastolic BP was 78.0 ± 7.5 . The pulse rate increased to 87.5 ± 11.4 at ten minutes ($+16.9 \pm 12.6\%$, $p < 0.001$) and fell to 76.7 ± 9.1 at 30 minutes ($p=ns$). Systolic BP increased to 122.3 ± 11.7 mm Hg at 10 minutes ($+2.73 \pm 5.1\%$, $p < 0.001$) and was 120.8 ± 10.8 at 30 minutes; while diastolic BP was 80.8 ± 7.3 at 10 minutes ($+3.83 \pm 6.1\%$, $p < 0.001$) and 79.4 ± 7.6 at 30 minutes.

Conclusion: Pan masala intake causes acute increase in pulse and BP.

106. Bhisey RA, Ramchandani AG, D'Souza AV, Borges AM, Notani PN.

Long-term carcinogenicity of pan masala in Swiss mice.

Int J Cancer. 1999 Nov 26;83(5):679-84.

Carcinogenesis Division, Cancer Research Institute, Tata Memorial Centre, Parel, Mumbai, India.

Carcinogenicity of pan masala, a dry powdered chewing mixture of areca nut, catechu, lime, spices and flavoring agents was evaluated by means of the long-term animal bio-assay 6- to 7-week old male and female S/RV Cri mice were divided randomly into intermediate and lifetime exposure groups and fed normal diet without pan masala (zero dose) or diet containing 2.5% and 5% pan masala. Animals in the intermediate-exposure group (n=10/gender/dose group) were killed after 6, 12 or 18 months of treatment, while those in the lifetime-exposure group (n=54/gender/dose group) were killed when moribund or at the termination of the experiment at 24 months. Several tissues were processed for histopathological examination. The body weight and survival rate of mice fed pan masala were lower than that of the controls. Histopathological observations of tissues from control animals did not reveal any neoplastic alterations. However, lifetime feeding of pan masala induced adenoma of the liver, stomach, prostate and sebaceous glands, also forestomach papilloma, liver hamartoma, hepatoma and hemangioma, carcinoma of the forestomach, adenocarcinoma of the lung and liver, and testicular lymphoma. Neoplastic lesions appeared mainly in the liver (n=13), stomach (n=3) and lung (n=8). Lung adenocarcinoma, the most frequent malignant tumor type, was observed in 2/120 mice in the intermediate-exposure group and in 8/216 animals in the lifetime-exposure group. Statistical analysis of tumor-induction data revealed a significant dose-related increase in lung adenocarcinomas but not in liver and stomach neoplasms indicating that lung is the major target tissue for the carcinogenic action of pan masala.

107. Chaudhry K.

Is pan masala-containing tobacco carcinogenic?

Natl Med J India. 1999 Jan-Feb;12(1):21-7

Indian Council of Medical Research, Ansari Nagar, New Delhi, India.

Background: Pan masala-containing tobacco (PM-T) was introduced in the Indian market during the 1970s. It is a mixture of areca nut, tobacco, lime, catechu and spices. Despite mounting evidence of health hazards of tobacco, tobacco manufacturers as well as policy-makers often seek evidence regarding the carcinogenicity of newer tobacco mixtures such as PM-T.

Methods: All the studies on pan masala (with or without tobacco) listed on MEDLARS, and the studies known to the expert committee on the subject constituted by the

Directorate General of Health Services, were reviewed. The studies on individual components and PM-T like substances were also reviewed. The interpretation of carcinogenicity of PM-T has been made, based on studies on (i) PM-T; (ii) PM-T like mixtures; and (iii) the effect of individual ingredients of PM-T and the likely effect of their combination.

Results: Studies on Chinese hamster ovary cells and Ames test indicate that PM-T is mutagenic. There is limited evidence that it may be carcinogenic to animals. The proportion of areca nut and tobacco in PM-T is in between the proportion of these substances in two known tobacco-areca nut mixtures of India (Mainpuri tobacco and mawa). Studies on Mainpuri tobacco indicate that it is carcinogenic, while literature suggests an association between mawa use and oral submucous fibrosis.

Conclusion: Human studies on PM-T like mixtures and the limited studies on PM-T suggest that PM-T is likely to be carcinogenic.

108. K. Kannan, A. K. Munirajan, J. Krishnamurthy, V. Bhuvaramurthy, B. K. Mohanprasad, K. H. Panishankar, N. Tsuchida, G. Shanmugam

Low incidence of p53 mutations in betel quid and tobacco chewing-associated oral squamous carcinoma from India

Int J Oncol. 1999 Dec;15(6):1133-6.

Cancer Biology Division, School of Biological Sciences, Madurai Kamaraj University, Madurai 625 021, India.

Mutations of the p53 tumor suppressor gene have been found to be the single most frequent event in human cancers. In India and other southeast Asian countries tobacco chewing with betel quid was attributed to be the major factor in oral carcinogenesis. We have analyzed 72 untreated primary oral squamous cell carcinomas (SCCs) for mutations in the tumor suppressor gene p53 exons 4-9 by PCR-SSCP and DNA sequencing. Sequencing analysis revealed 16 missense mutations, one silent mutation in codon 307 and four A to G substitution polymorphism in codon 213. The incidence of p53 mutation was 21% (15 of 72) excluding the polymorphism and the silent mutation. Eight mutations were clustered in codons 266-282 of exon 8. Of the total mutation events 37.5% were G to A transitions and 31.3% were G to T transversions. These results indicate the possible involvement of tobacco derived nitrosamines and their adducts in the genesis of oral cancer among Indians.

109. P. C. Gupta

Mouth cancer in India: a new epidemic?

J Indian Med Assoc. 1999 Sep;97(9):370-3.

Epidemiology Research Unit, Tata Institute of Fundamental Research, Mumbai.

Oral cancer has been traditionally described as a major form of cancer in India although on the basis of cancer registry data, it was thought that the incidence has decreased. There are several recent reports in the literature, however, predicting an increase in mouth cancer incidence in India. This prediction is based upon observation of an increasing prevalence of oral submucous fibrosis, especially in younger individuals, caused by gutka, an industrially manufactured food item. A comparison of the age distribution of recently reported oral submucous fibrosis cases and incident cases reported in the past clearly establishes that the disease is now occurring at much younger ages. A comparison of the age specific incidence rates of mouth cancer (ICD 143-5) during 1983-87 and 1995 in the city of Ahmedabad shows that the incidence has significantly increased in the younger population (< 50 years). Since tongue cancer (ICD 141) does not show a similar increase, it is concluded that the increase in mouth cancer incidence is real. Urgent public health measures are required to curb this new but avoidable epidemic.

110. Saranath D, Tandle AT, Teni TR, Dedhia PM, Borges AM, Parikh D, Sanghavi V, Mehta AR.

p53 inactivation in chewing tobacco-induced oral cancers and leukoplakias from India.

Oral Oncol. 1999 May;35(3):242-50

Laboratory of Cancer Genes, Tata Memorial Centre, Parel, Bombay, India.

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The inactivation of p53 tumour suppressor gene vis-à-vis point mutation, overexpression and degradation due to Human Papilloma virus (HPV) 16/18 infection, was examined in chewing tobacco-associated oral cancers and oral leukoplakias from India. The analysis of mutations was assessed by polymerase chain reaction (PCR) with single strand conformation polymorphism (PCR-SSCP) of exons 5-9 on DNA from 83 oral cancer cases, and the mutations confirmed by direct nucleotide sequencing of the PCR products. p53 protein expression was evaluated by immunohistochemical analysis on paraffin-embedded sections of 62 representative oral cancer biopsies and 22 leukoplakias, using p53-specific monoclonal antibody DO-7. The presence of HPV16/18 was detected in the 83 oral cancer cases by PCR analysis using HPV L1 consensus sequences, followed by Southern hybridization with type-specific oligonucleotide probes. Forty-six per cent (38/83) of oral cancer tumours showed p53 alterations, with 17% (14/83) showing point mutations, 37% (23/62) with overexpression and 25% (21/83) with presence of HPV16 wherein the E6 HPV16 protein degrades p53. HPV18 was not detected in any of the samples. Ninety-two per cent concordance was observed between missense point mutations and overexpression of p53 protein. A significant correlation was not observed between p53 alterations in oral cancer and clinico-pathological profile of the patients. Twenty-seven per cent (6/22) of oral leukoplakias

showed p53 overexpression. The overall p53 alterations in oral cancer tissues and oral lesions are comparable to data from the oral cancers reported in the Western countries with smoking and alcohol-associated oral cancers, and suggest a critical role for p53 gene in a significant proportion of oral cancers from India. The overexpression of p53 protein in leukoplakias may serve as a valuable biomarker for identifying individuals at high risk of transformation to malignant phenotype.

111. Warke RG, Kamat AS, Kamat MY.

Irradiation of chewable tobacco mixes for improvement in microbiological quality.

J Food Prot. 1999 Jun;62(6):678-81.

University Department of Chemical Technology, University of Mumbai, Matunga, India.

Microbiological quality of chewable tobacco mixes traditionally known as "Gutkha" was studied. The microbiological analysis of 15 samples analyzed revealed high bacterial and fungal counts. The total viable counts were in the range of $1.8 \times 10(4)$ to $7.2 \times 10(4)$ CFU g(-1) and the yeast and mold count from $3.6 \times 10(3)$ to $7.1 \times 10(4)$ CFU g(-1). The proteolytic and lipolytic counts were $9 \times 10(2)$ to $2.6 \times 10(3)$ CFU g(-1) and $2.6 \times 10(3)$ CFU g(-1), on an average, respectively. Lecithinase-positive *Staphylococcus aureus* was found in 2 of the 15 samples analyzed; the counts were up to $3.4 \times 10(3)$ CFU g(-1). Coliform and *Salmonella* spp. were found to be absent. Aflatoxins B₁, B₂, and G₂ were found to be present in all the samples. These samples were exposed to gamma radiation (⁶⁰Co) at 1-, 2-, 3-, 5-, 10-, and 25-kGy doses. The decrease in total viable count and fungal count was noticed with increase of radiation dose. The 3-kGy dose was observed to be the sterilization dose for Gutkha. At this dose no survival of organisms was noticed and no revival was observed during postirradiation storage at room temperature for 6 months.

112. Gupta PC, Sinor PN, Bhonsle RB, Pawar VS, Mehta HC

Oral submucous fibrosis in India: a new epidemic?

Natl Med J India. 1998 May-Jun;11(3):113-6.

Tata Institute of Fundamental Research, Maharashtra, India.

Background: Oral submucous fibrosis (OSF) is a precancerous condition caused by use of the areca nut. The reported prevalence of OSF in Bhavnagar district during 1967 was 0.16%. We investigated whether the impression of an increase in the incidence of the disease was real.

Methods: A house-to-house survey was conducted in Bhavnagar district, Gujarat state. The use of areca nut-containing products and tobacco was assessed through

an interviewer administered questionnaire. The oral examination was done by dentists. The diagnostic criteria for OSF was the presence of palpable fibrous bands.

Results: A total of 11,262 men and 10,590 women aged 15 years and older were interviewed for their tobacco habits. Among 5018 men who reported the use of tobacco or areca nut, 164 were diagnosed as suffering from OSF. All but four cases were diagnosed among 1786 current areca nut users (age-adjusted relative risk: 60.6). Areca nut was used mostly in mawa, a mixture of tobacco, lime and areca nut, and 10.9% of mawa users had OSF (age-adjusted relative risk: 75.6). The disease as well as areca nut use was concentrated (about 85%) in the lower (< 35 years) age group.

Conclusions: An increase in the prevalence of OSF, especially in the lower age groups, directly attributable to the use of areca nut products was observed. This could lead to an increase in the incidence of oral cancer in the future.

113. Gupta PC, Hebert JR, Bhonsle RB, Sinor PN, Mehta H, Mehta FS

Dietary factors in oral leukoplakia and submucous fibrosis in a population-based case control study in Gujarat, India

Oral Dis. 1998 Sep;4(3):200-6.

Epidemiology Research Unit, Tata Institute of Fundamental Research, Bombay, India.

Objectives: To investigate the relationship of specific nutrients and food items with oral precancerous lesions among tobacco users. **DESIGN:** A population-based case-control study.

Setting: Villages in Palitana taluk of Bhavnagar district, Gujarat, India.

Subjects and methods: An interviewer-administered food frequency questionnaire, developed and validated for this population, was used to estimate nutrient intake in blinded, house-to-house interviews. Among 5018 male tobacco users, 318 were diagnosed as cases. An equal number of controls matched on age (± 5 years), sex, village, and use of tobacco were selected.

Main outcome measures: Odds ratios (OR) from multiple logistic regression analysis controlling for relevant variables (type of tobacco use and economic status).

Results: A protective effect of fibre was observed for both oral submucous fibrosis (OSF) and leukoplakia, with 10% reduction in risk per g day⁻¹ ($P < 0.05$). Ascorbic acid appeared to be protective against leukoplakia with the halving of risk in the two highest quartiles of intake (versus the lowest quartile: OR=0.46 and 0.44, respectively; $P < 0.10$). A protective effect of tomato consumption was observed in leukoplakia and a suggestion of a protective effect of wheat in OSF.

Conclusions: In addition to tobacco use, intake of specific nutrients may have a role in the development of oral precancerous lesions.

114. M. M. Vaidya, S. S. Sawant, A. M. Borges, S. B. Ogale, A. N. Bhisey

Cytokeratin expression in precancerous lesions of the human oral cavity

Oral Oncol. 1998 Jul;34(4):261-4.

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Cytokeratin (CK) expression was studied in buccal mucosa (BM) from 20 leucoplakia and 7 submucous fibrosis patients using sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), immunoblotting and two-dimensional gel electrophoresis with iso-electric focussing (IEF) as the first dimension. Normal BM expresses CK 4, 5, 13, 14 and perhaps 19. Of 20 leucoplakia samples analysed, CK 5 was not detected in 17 samples, while CK 14 was not found in 13 samples. CK 1 and CK 8 were aberrantly expressed in six and seven samples, respectively. CK expression in contralaterally collected uninvolved tissues from 3 patients showed a normal pattern in two samples. Non-expression of CK 5 was observed in five of seven submucous fibrosis samples, while CK 14 was not detected in only two samples. CK 8 was aberrantly expressed in three samples. All the leucoplakia patients were chronic tobacco chewers. Thus, non-expression of CK 5 may be an early event occurring in tobacco-associated pathological changes in the BM.

115. Misra SP, Misra V, Dwivedi M, Gupta SC.

Oesophageal subepithelial fibrosis: an extension of oral submucosal fibrosis.

Postgrad Med J. 1998 Dec;74(878):733-6.

MLN Medical College, Department of Gastroenterology, India.

Fifty-five patients with oral submucosal fibrosis and an equal number of patients with no evidence of the disease were studied. All patients underwent upper gastrointestinal endoscopy and any abnormality was noted. Multiple oesophageal biopsies were obtained from the upper end of the oesophagus and from any endoscopically observed abnormality. The histological changes in the two groups were assessed blindly by an experienced histopathologist. Histological abnormalities were noted in the oesophageal mucosa in 2% of controls and 66% of patients with oral submucosal fibrosis ($p < 0.0001$). In the control group, acanthosis was seen in one patient, while in the patient group atrophy of the squamous epithelium was evident in 52%, hyperkeratosis in 52%, parakeratosis in 30%, dyskeratosis in 14%, acanthosis in 14%, and papillomatosis and mild dysplasia in 2% patients. Subepithelial collagenization was seen in 32 (64%) patients. The oesophageal abnormalities were seen more frequently in patients who had consumed Pan masala, Gutka, betel nut, tobacco or a combination of some or all of these, with or without betel leaf, for ≥ 5 years compared to those consuming them for a

shorter period of time (91% vs 46%, $p < 0.001$). It is concluded that oral submucosal fibrosis is not a disease confined to the oral cavity; the oesophagus may also be involved in about two-thirds of patients.

116. Patel RK, Trivedi AH, Jaju RJ, Kukreti MS, Bhatavdekar JM, Shah PM, Patel DD.

Protection from pan masala induced genomic damage by beta-carotene and retinoic acid--an in vitro experience.

Neoplasma. 1998;45(3):169-75.

Cell Biology Division, Gujarat Cancer Society, Asarwa, Ahmedabad, India.

Cytogenetic studies in Chinese hamster ovary (CHO) cells using aqueous and organic extracts of pan masalas, as well as genomic damage observed among pan masala consumers have conclusively shown genotoxic potential of pan masala—a dry complex mixture of areca nut, lime, catechu, cardamom, unspecified flavoring agent, etc., often containing tobacco in it. Tobacco and areca nut, major ingredients of pan masala, are closely associated with oral cancer. The most widely studied group of compounds in the field of chemoprevention is retinoids which includes natural vitamin A, beta-carotene and synthetic derivatives of vitamin A. In the present study, antigenotoxic effect of beta-carotene (BC) and retinoic acid (RA) on genotoxic potential of pan masala have been evaluated in CHO cells with the help of sister chromatid exchange (SCE) frequency and chromosome aberration (CA) frequency as cytogenetic markers. The pulse treatment with pan masala plain/pan masala-tobacco (PM/PMT) extract in combination with either BC or RA yielded lower frequencies of CA and SCE in CHO cells as compared to the cultures treated with aqueous extract of pan masalas alone. This antigenotoxic effect of BC and RA was more pronounced when treatment was given continuously for a longer duration. Thus, these results indicated possibility of using BC and RA to decrease the risk of oral cancer among pan masala chewers.

117. Patel RK, Trivedi AH, Roy SK, Bhatavdekar JM, Shah PM, Patel DD.

Influence of alpha-tocopherol and ascorbic acid on pan masala induced genomic damage. An in vitro experiment.

J Exp Clin Cancer Res. 1998 Dec;17(4):419-24.

Department of Cancer Biology, The Gujarat Cancer and Research Institute, Asarwa, Ahmedabad, India.

Pan masala is a dry complex mixture of areca nut, catechu, lime, cardamom, unspecified flavouring agents etc., with (PMT) or without tobacco (pm). We have previously reported genotoxic potential of tobacco, areca nut and pan masala per se. An antigenotoxic effect of alpha-tocopherol (AT) and ascorbic acid (AA) against the PM/PMT induced genotoxic on Chinese hamster ovary (CHO) cells have been studied using chromosome aberration (CA) assay. AT and AA, per se, had no effect on CA frequency at the concentrations

used in the present study. The short-term treatment of AT with aqueous extracts of PM/PMT yielded lower frequencies of CA as compared to the cultures treated with aqueous extracts of PM/PMT alone. However, a statistically significant reduction in CA frequency was observed with continuous treatment only. AA had no statistically significant protective effect except for continuous treatment with 10 ug/ml AA against the aqueous extract of PMT. The results indicate the possible use of AT to reduce the risk of oral cancer among PM/PMT chewers.

118. P. Pande, M. Mathur, N. K. Shukla, R. Ralhan

pRb and p16 protein alterations in human oral tumorigenesis
Oral Oncol. 1998 Sep;34(5):396-403.

Department of Biochemistry, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

Cyclin dependent kinase inhibitor 2/multiple tumour suppressor gene 1 (CDKN2/MTS1) and retinoblastoma (Rb) tumour suppressor genes play important roles in the regulation of the cell cycle. The protein products of these genes p16INK4 (p16) and pRb, respectively, like p53 protein inhibit progression from G1 to S phase. p16 exerts its function through inhibition of CDK4-mediated phosphorylation of pRb. The pRb/p16 pathway is a critical target for molecular aberration at the G1-S checkpoint in a wide range of primary human tumours. The expression of p16 and pRb proteins was analyzed by immunohistochemistry in 35 cases of oral squamous cell carcinomas (SCCs), 22 cases of premalignant oral lesions and 30 normal oral tissues. Lack of pRb expression was observed in 23/35 (66%) oral SCCs and 14/22 (64%) premalignant lesions. Lack of p16 expression was observed in 22/35 (63%) oral SCCs and 13/22 (59%) premalignant lesions. Weak p16 and pRb immunoreactivities were observed in normal oral mucosal epithelium. The status of p16 and pRb was correlated with clinicopathological characteristics of the patients. Alteration in p16 expression showed significant correlation with tumour staging and progression ($P = 0.024$). Alteration in pRb/p16 expression correlated with heavy consumption of betel and tobacco. Our results suggest that alterations in the p16/pRb pathway are early events in oral tumorigenesis and may be involved in the development of betel- and tobacco-related oral malignancies.

119. P. R. Murti, K. A. Warnakulasuriya, N. W. Johnson, R. B. Bhonsle, P. C. Gupta, D. K. Daftary, F. S. Mehta

p53 expression in oral precancer as a marker for malignant potential

J Oral Pathol Med. 1998 May;27(5):191-6.

Basic Dental Research Unit and WHO Collaborating Centre for Oral Cancer Prevention, Tata Institute of Fundamental Research, Bombay, India.

The potential of p53 protein expression as a marker for determining which oral precancerous lesions may transform to malignancy with time was assessed. We compared the p53 expression in archival formalin-fixed, paraffin-embedded tissues from 22 baseline biopsies of precancerous lesions that transformed to cancer in 4-25 years against that in 68 similar lesions that did not transform over the same time period. Twenty-nine percent of precancers that transformed were p53-positive at baseline, compared to 31% of the biopsies that did not transform to malignancy. When examined by immunohistochemical methods p53 expression failed to detect potential malignant status of oral precancer. Non-specificity of the assay may account for this result but overexpression of p53 due to DNA damage by tobacco/betel-quinid in non-progressive lesions needs further study. Nine precancerous lesions became p53-immunoreactive from precancer to cancer. This may suggest p53 overexpression peaks close to the time of transition from precancer to cancer rather than early in the natural history of oral precancer.

120. Ramchandani AG, D'Souza AV, Borges AM, Bhisey RA

Evaluation of carcinogenic/co-carcinogenic activity of a common chewing product, pan masala, in mouse skin, stomach and esophagus.

Int J Cancer. 1998 Jan 19;75(2):225-32.

Carcinogenesis Division, Cancer Research Institute, Tata Memorial Centre, Parel, Mumbai, India.

Pan masala, a dry powdered mixture of areca nut, catechu, lime, unspecified spices and flavoring agents, has gained widespread popularity as a chewing substitute in India. In this study, the carcinogenic and tumor-promoting potential of an ethanolic pan masala extract (EPME) was determined using skin of S/RVCri-ba mice and forestomach and esophagus of ICRC mice as the target tissues. Carcinogenic activity of pan masala was tested by painting the mouse skin for 40 weeks with EPME or by gavage feeding for 6 months. Following initiation with 9,10-dimethylbenz(a)anthracene (DMBA), carcinogenesis of mouse skin was promoted with different doses of EPME, while gastric- and esophageal-tumor-promoting activity was determined by administering EPME by gavage to animals initiated with diethylnitrosamine (DEN). The ability of EPME to effect progression of skin papilloma to carcinoma and cutaneous alterations after a single or multiple EPME treatment were also evaluated. EPME at 25 mg per dose promoted skin-papilloma formation between 30 and 40 weeks of treatment and enhanced the rate of conversion of papilloma to carcinoma. Induction of mild epidermal hyperplasia, dermal edema, increase in epidermal mitotic activity and the rate of epidermal and dermal DNA synthesis by EPME correlated well with its skin-tumor-promoting potential. In ICRC

mice, EPME was inactive as a complete carcinogen, but effectively promoted the development of forestomach and esophageal papilloma and carcinoma in a concentration-dependent manner. The tumor incidence at 25 mg EPME per dose was comparable with that obtained in the 12-O-tetradecanoylphorbol-13 acetate(TPA)-treated group. The findings indicate that habitual pan-masala use may exert carcinogenic and co-carcinogenic influence.

121. R. Ralhan, N. Nath, S. Agarwal, M. Mathur, B. Wasylyk, N. K. Shukla

Circulating p53 antibodies as early markers of oral cancer: correlation with p53 alterations

Clin Cancer Res. 1998 Sep;4(9):2147-52.

Department of Biochemistry, All India Institute of Medical Sciences, Ansari Nagar, New Delhi

p53 aberrations are early events in the pathogenesis of betel- and tobacco-related oral malignancies. Accumulation of p53 protein in oral lesions may elicit a humoral immune response against p53 protein in these patients. p53 antibodies (Abs) were analyzed in 183 sera obtained from patients with premalignant or malignant oral lesions and normal individuals by enzyme-linked immunoassay using recombinant p53 protein as antigen. These results were correlated with accumulation of p53 protein in patients' matched oral tissue specimens. Circulating p53 Abs were observed in 24 of 70 (34%) cancer patients and 15 of 50 (30%) patients with premalignant oral lesions. p53 Abs showed a significant association with increase in tumor size and dedifferentiation of tumors, factors indicative of poor prognosis. Expression of p53 protein was analyzed in 43 matched oral lesions (18 premalignant and 25 malignant cases). All the p53-seropositive patients (7 leukoplakia and 11 squamous cell carcinoma) showed elevated levels of p53 protein in matched oral lesions. However, the total number of patients seropositive for p53 Abs was lesser than that of patients exhibiting p53 protein accumulation in oral lesions. Four of the 63 normal healthy individuals who were heavy consumers of tobacco (smoking/chewing) and betel were found to be positive for p53 Abs. Detection of circulating p53 Abs in patients with premalignant oral lesions suggests that humoral immune response against p53 protein is an early event in oral oncogenesis and may be a surrogate marker for both p53 alteration and preclinical cancer.

122. Shah N, Sharma P. P.

Role of chewing and smoking habits in the etiology of oral submucous fibrosis (OSF): a case-control study

J Oral Pathol Med. 1998 Nov;27(10):475-9.

Department of Dental Surgery, All India Institute of Medical Sciences, New Delhi.

Oral submucous fibrosis (OSF), a premalignant and crippling condition of the oral mucous membrane, was studied to identify its relationship to various chewing and smoking habits. Two hundred and thirty-six consecutive cases of OSF were compared with 221 control subjects matched for age, sex and socio-economic conditions. It was found that chewing of areca nut/quid or pan masala (a commercial preparation of areca nuts, lime, catechu and undisclosed colouring, flavouring and sweetening agents) was directly related to OSF. Also, pan masala was chewed by a comparatively younger age group and was associated with OSF changes earlier than areca nut/quid chewing. However, chewing or smoking tobacco with various other chewing habits did not increase the risk of developing OSF. It was also found that frequency of chewing rather than the total duration of the habit was directly correlated to OSF.

123. Singh A, Singh SP.

Postnatal effect of smokeless tobacco on phytic acid or the butylated hydroxyanisole-modulated hepatic detoxication system and antioxidant defense mechanism in suckling neonates and lactating mice.

Cancer Lett. 1998 Jan 9;122(1-2):151-6

Human Genetics Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India.

The present study evaluates the potential of smokeless tobacco to trans-lactationally modify the chemopreventive efficacy of phytic acid and butylated hydroxyanisole (BHA) via modulation of the hepatic xenobiotic detoxication system and antioxidant defense mechanism in the murine system. Phytic acid (1000 mg/kg b.w./day) by gavage while BHA (1% w/w) in diet induced a significant increase in the levels of glutathione-S-transferase (GST), acid soluble sulfhydryl (-SH), cytochrome b5 (Cyt. b5) and cytochrome P-450 (Cyt. P-450) in lactating dams and suckling pups. The hepatic levels of GST and -SH were significantly depressed whereas microsomal Cyt. b5, Cyt. P-450 and MDA levels were elevated in groups treated with smokeless tobacco (50 or 100 mg/kg b.w./day). The data reveals the inhibitory potential of smokeless tobacco on phytic acid-induced GST/GSH system efficiency besides the significant augmentation by smokeless tobacco on phytic acid or BHA-induced microsomal phase I enzymes. The direct or trans-lactational modulation in the levels of xenobiotic detoxication system enzymes suggests the potential of smokeless tobacco to modify the chemopreventive efficacy of phytic acid or BHA.

124. Verma A.

Cytogenetic investigations on patients with oral submucous fibrosis

J Indian Med Assoc. 1998 Feb;96(2):51-2, 57.

Department of Genetics, National Dairy Research Institute, Karnal.

Lymphocyte cultures were set up from venous blood samples collected from 23 patients of submucous fibrosis (SMF) and 10 normal controls. Slides, thus prepared, were processed and screened for G-, C-banding and sister chromatid exchange (SCE) frequency analysis. No gross chromosomal anomalies except that a few breaks and gaps were observed to be randomly distributed throughout the genome. However, a proportionate increase in SCE frequency in SMF patients as compared to the normal control individuals was observed. An attempt has been made to correlate the period of betel leaves, nuts, quid and tobacco chewing with the incidence of chromosomal anomalies and increase in SCE frequency and its sexwise distribution in these patients.

125. Kannan A, Das M, Khanna SK.

Estimation of menthol in Pan Masala samples by a spectrophotometric method.

Food Addit Contam. 1997 May-Jun;14(4):367-71.

Food Toxicology Division, Industrial Toxicology Research Centre, Lucknow, India.

Recently, the Prevention of Food Adulteration Act of India has fixed the level of menthol addition to Pan Masala at 0.1%, therefore good manufacturing practice (GMP) should be adopted so that the samples do not exceed 0.1% menthol (1 mg/g). The estimation of menthol in Pan Masala samples involves steam distillation followed by reaction with p-dimethyl amino benzaldehyde (DMAB) in acidic medium to give a red colour, which is read at 550 nm. The sensitivity of this procedure is 75 micrograms menthol per g sample. Using this method, 130 branded and 53 non-branded samples of Pan Masala were analysed for menthol content. Almost 25% of branded samples contained less than 1 mg menthol per g while 75% of samples contained 1.1-6.5 mg menthol per g Pan Masala. Non-branded Pan Masala contained 1 mg menthol per g in only 7.6% of samples. However, 92% of samples contained 1.1-6.5 mg menthol per g, suggesting that the addition of menthol is relatively higher in non-branded Pan Masala samples than in branded ones.

126. Singh A, Singh SP.

Modulatory potential of smokeless tobacco on the garlic, mace or black mustard-altered hepatic detoxication system enzymes, sulfhydryl content and lipid peroxidation in murine system.

Cancer Lett. 1997 Sep 16;118(1):109-14

School of Life Sciences, Jawaharlal Nehru University, New Delhi, India.

The present study evaluates the potential of smokeless tobacco to modify the chemopreventive efficacy of minor dietary constituents, including garlic, mace or black mustard, via modulating the competing pathways of hepatic detoxication system and antioxidant defense mechanism in murine system. Garlic (100 mg/kg b.w. per day) by gavage and mace (1% w/w) or black mustard (1% w/w) in diet induced a significant increase in the levels of glutathione-S-transferase (GST), acid-soluble sulfhydryl (-SH), cytochrome b5 (Cyt.b5) and cytochrome P-450 (Cyt.P-450) in murine liver. The hepatic levels of GST and -SH were significantly depressed whereas microsomal Cyt.b5, Cyt.P-450 and MDA levels were elevated in groups treated with smokeless tobacco (50 or 100 mg/kg b.w. per day). The data revealed the inhibitory potential of smokeless tobacco on garlic-induced hepatic GST/GSH system besides the significant augmentation by smokeless tobacco on garlic or mace or black mustard-induced microsomal cytochromes. The possible implications of modulation in competing bioactivation and detoxication pathways in the process of chemical carcinogenesis are discussed.

127. Babu S, Bhat RV, Kumar PU, Sesikaran B, Rao KV, Aruna P, Reddy PR.

A comparative clinico-pathological study of oral submucous fibrosis in habitual chewers of pan masala and betelquid.

J Toxicol Clin Toxicol. 1996;34(3):317-22.

Food Toxicology Research Centre, National Institute of Nutrition, Hyderabad, India.

Background: Oral submucous fibrosis associated with chewing of betel nut products has an estimated prevalence of 0.2-1.2% in India. The increasing use of pan masala/gutkha, a mix of tobacco and a less moist form of betelquid lacking the betel leaf, seems associated with an earlier age of onset of oral submucous fibrosis.

Method: A prospective study examined the in vivo effects of pan masala/gutkha and betelquid chewing on buccal mucosal cytology in 50 patients with oral submucous fibrosis and 40 controls.

Results: The percentage of nucleolated intermediate cells or proliferative fraction of buccal mucosa cells was significantly higher in all habitual chewers than controls. Pan masala/gutkha chewers presented with oral submucous fibrosis after 2.7 ± 0.6 y of use whereas the betelquid users presented with oral submucous fibrosis reported 8.6 ± 2.3 y of use ($p < 0.05$).

Conclusions: Habitual chewing of pan masala/gutkha is associated with earlier presentation of oral submucous fibrosis than betelquid use. Factors which may be responsible for these differences are the tobacco content, the absence of the betel leaf and its carotenes and the much higher dry weight of pan masala/gutkha.

128. Ghosh S, Shukla HS, Mohapatra SC, Shukla PK.
Keeping chewing tobacco in the cheek pouch overnight (night quid) increases risk of cheek carcinoma.

Eur J Surg Oncol. 1996 Aug;22(4):359-60.

Department of Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

Chewing Chewable Indian Tobacco (CIT) is a popular addiction in India. Some of the addicts keep the bolus of chewed tobacco tucked in the gingivo-labial sulcus (cheek pouch) overnight. This is known as the habit of the night quid. To assess the influence of night quid on the development of oral cancer we carried out this case control observational study in the Out Patient Department of Surgery, Sir Sunder Lai Hospital, Varanasi, India. A total of 105 consecutive oral cancer patients (epidermoid carcinoma) and 71 sex- and age-matched CIT addicts of the same duration of addiction were investigated for the habit of the night quid. The habit increased the risk of development of cheek carcinoma significantly at Odd's Ratio of 12.5. Simply giving up the habit of night quid could help in the reduction of oral cancer in CIT addicts.

129. K. Shankaran, S. V. Kandarkar, Q. Q. Contractor, R. H. Kalro, H. G. Desai
Electron microscopic observations in gastric mucosa of habitual tobacco chewers

Indian J Med Res. 1994 Jun;99:267-71.

Department of Gastroenterology, B.Y.L. Nair Ch. Hospital, Cancer Research Institute, Bombay.

Clinical evaluation, upper gastrointestinal endoscopy and electron microscopy of mucosal biopsies from antrum, body and fundus of stomach were performed in three control subjects and 17 habitual tobacco chewers. Electron microscopic abnormalities such as discontinuous, fragmented basement membrane with reduction in hemidesmosomes, and widened intercellular spaces filled with clusters of desmosomes were found in the gastric mucosa of habitual tobacco chewers; these were similar to those reported in experimental carcinogenesis and leukoplakia. It is concluded that habitual chewing of tobacco produces electron microscopic alterations in the human gastric mucosa which may be important precursors for gastric malignancy.

130. M. P. Niphadkar, Q. Q. Contractor, R. A. Bhisey
Mutagenic activity of gastric fluid from chewers of tobacco with lime

Carcinogenesis. 1994 May;15(5):927-31.

Carcinogenesis Division, Tata Memorial Centre, Parel, Bombay, India.

Although tobacco chewing is strongly associated with a high risk of oral and upper alimentary tract cancers, the nature of mutagenic exposure among users has not been clearly defined. In this study, tobacco-specific and mutagenic exposure of chewers of tobacco with lime was evaluated by analysis of gastric fluid (GF). The pH, nitrite and cotinine levels of GF samples from chewers and non-chewers were determined and the samples were tested for mutagenicity in the Ames Salmonella/microsome assay using Salmonella typhimurium strains TA98, TA100 and TA102. Cotinine was not detected in GF from non-chewers while the levels ranged between 0.4-13.64 µg/ml in samples from chewers; however, the mean pH values (3.8 ± 0.4 versus 2.8 ± 0.3) and nitrite levels (29.40 ± 1.51 versus 27.39 ± 0.83 µM) were similar in both groups. While all GF samples from non-chewers were non-mutagenic, samples from chewers were directly mutagenic or upon nitrosation to all the three tester strains and to TA102 strain in the presence of S9. Experiments using scavengers of reactive oxygen species (ROS) showed that mannitol and benzoate abolished the mutagenic response of TA102, indicating that ROS are principally responsible for oxidative damage. The findings provide specific information regarding the mutagenic exposure among tobacco chewers and suggest that tobacco chewing may be an important risk factor in the development of gastric cancer.

131. Patel RK, Jaju RJ, Bakshi SR, Trivedi AH, Dave BJ, Adhvaryu SG.

Pan masala--a genotoxic menace.

Mutat Res. 1994 Feb;320(3):245-9.

Cell Biology Division, Gujarat Cancer Society, Ahmedabad, India.

Cytogenetic markers such as chromosome aberration (CA), sister-chromatid exchange (SCE) and micronucleated cells (MNC) were used to assess the genotoxic potential of dimethyl sulphoxide (DMSO) extract of pan masala with and without tobacco (PM-T and PM). Using in vitro short-term assays, the extracts were tested in the presence or absence of metabolic activation. In cultures without metabolic activation the extracts were found to increase the frequency of all the three parameters tested significantly, however those with activation elicited a weak response, implying that pan masalas contain solvent (DMSO)-soluble direct-acting mutagen.

132. Patel RK, Trivedi AH, Jaju RJ, Adhvaryu SG, Balar DB.

Ethanol potentiates the clastogenicity of pan masala--an in vitro experience.

Carcinogenesis. 1994 Sep;15(9):2017-21.

Cell Biology Division, Gujarat Cancer Society, Ahmedabad, India.

The significance of the interaction between alcohol and tobacco in causing head and neck cancers is well documented. Our previous reports on in vitro studies using aqueous and organic extracts as well as cytogenetic studies among pan masala consumers have conclusively shown the genotoxic potential of pan masala—a dry mixture of the areca nut, lime, catechu, unspecified flavouring agents, etc., often containing tobacco in it and is widely consumed in India. Now in the present report, the clastogenic effect of ethanol and pan masala in different combinations was evaluated on Chinese hamster ovary cells utilizing chromosome aberration (CA) frequency as an endpoint. An ethanol concentration of up to 2.0% had no effect on CA/cell value. The low-dose continuous treatment and high-dose short-term pre-, post- and simultaneous treatment of ethanol and aqueous extract of pan masala with and without tobacco yielded dose-dependent elevations in CA frequency, compared to any of these two substances alone. Thus, these results provide evidence that alcohol consumption may potentially increase the risk of oral cancer among pan masala chewers

133. Trivedi AH, Patel RK, Rawal UM, Adhvaryu SG, Balar DB.

Evaluation of chemopreventive effects of betel leaf on the genotoxicity of pan masala.

Neoplasma. 1994;41(3):177-81.

Cell Biology Division, Gujarat Cancer Society, Ahmedabad, India.

The antigenotoxic effect of the aqueous extract of betel leaf (BL-ext.) against the pan masala was tested with the help of cytogenetic endpoints like chromosome aberration (CA) and sister chromatid exchange (SCE) utilizing Chinese hamster ovary (CHO) cells. Compared to the cultures treated with aqueous extract of pan masala alone, a reduction in CA and SCE frequencies in CHO cells was observed following a combined treatment with pan masala (with or without tobacco) extract and BL-ext. The protective effect of BL-ext. against the genomic damage caused by pan masala was statistically significant only after treating the cells for a longer period.

134. H. Trivedi, B. J. Dave, S. G. Adhvaryu

Genotoxic effects of tobacco extract on Chinese hamster ovary cells

Cancer Lett. 1993 Jun 15;70(1-2):107-12.

Cell Biology Division, Gujarat Cancer and Research Institute, Ahmedabad, India.

Genotoxic effects of an aqueous extract of *Nicotiana tabacum*, a variety commonly used in India for chewing purposes, were analysed on CHO cells utilizing two different cytogenetic end-points, namely, chromosome aberration frequency and sister chromatid exchange frequency. Statistically significant elevations in the values of both

the markers clearly indicated chromosome damaging effects of the extract. Elevations in chromosome aberration and sister chromatid exchange frequencies are suggestive of intrastrand and interstrand DNA cross-links following exposure to tobacco. The effects observed following treatment with low dose for longer duration are of relevance to the condition of the oral mucosa of the chronic smokeless tobacco users.

135. H. Trivedi, B. J. Dave, S. G. Adhvaryu

Monitoring of smokeless tobacco consumers using cytogenetic endpoints

Anticancer Res. 1993 Nov-Dec;13(6A):2245-9.

Cell Biology Division, Gujarat Cancer Society, Ahmedabad, India.

Smokeless tobacco consumption is causally associated with oral cavity cancers; however, extensive cytogenetic studies have not been done. In the present study, individuals consuming dry snuff or tobacco with lime have been studied for frequency of micronucleated cells (MNC) in exfoliated buccal mucosa and chromosome aberrations (CA) and sister chromatid exchanges (SCE) in lymphocytes. The significant elevation in the values of all the three cytogenetic markers among tobacco users compared to the controls reveal the extent of genomic damage on target and nontarget tissues. The findings emphasize the possible use of cytogenetic endpoints for monitoring smokeless tobacco consumers.

136. Anuradha CD, Devi CS.

Serum protein, ascorbic acid & iron & tissue collagen in oral submucous fibrosis--a preliminary study.

Indian J Med Res. 1993 Jun;98:147-51.

Department of Biochemistry, University of Madras.

A study of 36 patients with oral submucous fibrosis, revealed that all patients had the habit of chewing betel nut, pan masala or the traditional mixture (betel nut, betel leaf and lime) suggesting a link between fibrosis and arecanut. There was an increase in the globulin fraction of protein and hence a decreased A/G ratio in these patients. There was a significant increase in total protein levels possibly due to the increase in globulin fractions and other serum proteins. Ascorbate and iron levels decreased perhaps because of their utilisation in collagen synthesis. The total tissue collagen content increased significantly in patients with advanced disease and, it increased with the progression of the disease leading to hypomobility of the tongue, lips, cheeks, soft palate and faucial pillars.

137. D. Saranath, L. T. Bhoite, M. G. Deo

Molecular lesions in human oral cancer: the Indian scene

Eur J Cancer B Oral Oncol. 1993 Apr;29B(2):107-12.

Cell and Developmental Pathology Division, Cancer Research Institute, Bombay, India.

Carcinogenesis is a multi-step process including aberrant expression of two interacting classes of genes--oncogenes and tumour suppressor genes. With recent technological advances, it is feasible to identify the various molecular lesions underlying the different stages of neoplasia. Squamous cell carcinomas of the head and neck, although representing 2-4% of the malignancies in the West, comprise a large fraction (40%) of total cancers in India, posing a major health problem. Further, epidemiological and experimental evidence unequivocally confirms a causal association between tobacco chewing habit, highly prevalent in India, and oral cancers. Thus, the oral cancers offer an excellent *in vivo* system for the study of the environmental tobacco-carcinogen induced molecular alterations in the malignancy, and associated premalignant lesions such as leukoplakia. With a view to elucidating the molecular lesions involving oncogenes in oral carcinogenesis, we have investigated *myc/ras/EGF-R* activation by amplification, point mutation, gene rearrangement and allelic losses. Further, a functionally activated potent transforming gene was detected in a NIH3T3 transfection/tumorigenicity assay, unrelated to *myc/ras/EGF-R*. Studies on the involvement of p53 gene in oral cancer, indicates p53 allelic loss as an event observed in leukoplakia and tumour tissues. Advanced oral cancer stages demonstrate cumulative molecular aberrations, with greater than 95% samples showing oncogene involvement, thus indicating a multi-step process of oral carcinogenesis. The review presents a comparative picture of the oral malignancies seen in Western countries and India, significance of molecular lesions and future perspectives of oncogenes and tumour suppressor gene involvement in oral cancer.

138. J. J. Kayal, A. H. Trivedi, B. J. Dave, J. Nair, U. J. Nair, S. V. Bhide, U. C. Goswami, S. G. Adhvaryu
Incidence of micronuclei in oral mucosa of users of tobacco products singly or in various combinations
Mutagenesis. 1993 Jan;8(1):31-3.

Carcinogenesis Division, Cancer Research Institute, Tata Memorial Centre, Parel, Bombay, India.

Frequencies of micronucleated cells (MNCs) were analyzed in the exfoliated buccal mucosa of normal healthy individuals from different parts of India who were regularly using either areca nut alone, mava, tamol, tobacco with lime, dry snuff or masher. The analyses were also carried out among oral submucous fibrosis patients who had the habit of chewing either mava or areca nut. Compared with 'no habit' healthy

individuals, all the groups, irrespective of their type of habit, had significantly higher frequencies of MNCs.

139. K. Shankaran, S. V. Kandarkar, Q. O. Contractor, R. H. Kalro, H. G. Desai
Ultrastructural changes in esophageal mucosa of chronic tobacco chewers

Indian J Med Res. 1993 Feb;98:15-9.

Department of Gastroenterology, BYL Nair Ch. Hospital, T.N. Medical College, Bombay.

Seventeen chronic tobacco chewers and three control subjects underwent clinical evaluation, upper gastrointestinal endoscopy and esophageal mucosal biopsies. The esophageal biopsies were processed and examined under the electron microscope. A large number of ultrastructural abnormalities such as discontinuous, fragmented basement membrane, with reduction in hemidesmosomes, widened intercellular spaces were found in the esophageal mucosa of chronic tobacco chewers which resembled the ultrastructural features of experimental carcinogenesis and leukoplakia. It is concluded that chronic chewing of tobacco produces ultrastructural abnormalities in the esophageal mucosa which could be important precursors for esophageal malignancy.

140. Polasa K, Babu S, Shenolikar IS..
Dose-dependent genotoxic effect of pan masala and areca nut in the Salmonella typhimurium assay.

Food Chem Toxicol. 1993 Jun;31(6):439-42

National Institute of Nutrition, Jamai-Osmania, Hyderabad, India.

Aqueous extracts of different brands of pan masala and scented supari were tested for mutagenicity by the Salmonella typhimurium assay using tester strains TA98 and TA100. These extracts were found to be mutagenic to both tester strains. The mutagenic effects of pan masala and scented supari extracts were similar to that produced by areca nut extract. The addition of 500 ppm saccharin to the supari extracts did not alter the mutagenic response.

141. R. B. Govekar, R. A. Bhisey
Mutagenic activity in urine samples from female tobacco habitués

Cancer Lett. 1993 Apr 30;69(2):75-80.

Carcinogenesis Division, Tata Memorial Centre, Parel, Bombay, India.

Since high incidence of oral cancer in India is associated with smokeless tobacco usage, mutagenic exposure of subjects habituated to a pyrolysed tobacco product,

masheri (M) and tobacco-containing betel quid (Q) was evaluated in the present study. Urinary cotinine was estimated to ascertain tobacco exposure and urine mutagenicity to Salmonella typhimurium TA98 and TA100 was used to assess mutagenic burden. Urinary cotinine levels were higher in MQ users than in M users. Urine mutagenicity was evident in control samples only upon treatment with S9, beta-glucuronidase or acidified nitrite. However, greater exposure of users to mutagens resulted in additional direct mutagenicity to TA100.

142. S. Krishnamurthy, S. Joshi

Gender differences and low birth weight with maternal smokeless tobacco use in pregnancy

J Trop Pediatr. 1993 Aug;39(4):253-4.

National Cancer Registry Project (ICMR), Tata Memorial Hospital Annexe, Bombay, India.

A preliminary study of maternal smokeless tobacco use, mostly oral applications of burnt tobacco or 'mishri', in pregnancy showed 65 of 178 singleton liveborns occurred to users and 113 to non-users in Bombay, India. Eighty-three newborns, 42 to maternal tobacco users and 41 to non-users were < 2.5 kg birth weight, i.e. low birth weight (LBW; odds ratio 3.2; confidence interval 1.5-6.9; $P < 0.001$). Stratifying by gender yielded odds ratios of 1.6 ($P > 0.1$, NS) for male and 6.96 (confidence interval 2.5-19.4, $P < 0.0005$), for female newborns compared to normal birthweight boys and girls, respectively. Male:female newborns were 80.6:100 in maternal tobacco users compared to 105.5:100 in non-users. Defining LBW as < 2.0 kg yielded an odds ratio of 5.4 (confidence interval 1.8-15.2, $P < 0.005$) in maternal tobacco users' offspring. For babies weighing 2-2.5 kg at birth it was 2.76 (confidence interval 1.4-5.5, $P < 0.01$). Maternal use of 'mishri' tobacco in pregnancy may be associated with (1) the offsprings' low birth weight, (2) low birth weights in girls more than in boys; (3) decreased male:female ratio in live newborns, and (4) low birth weight of < 2.0 kg more than of 2-2.5 kg. Studies are needed to substantiate these findings. Gender differences in outcome suggest the in utero effect of maternal smokeless tobacco use on male and female fetuses may differ.

143. Dash BC, Das RK.

Genotoxicity of 'gudakhu', a tobacco preparation. I. In mice in vivo.

Mutat Res. 1992 Jul;280(1):45-53.

Environmental Mutagenesis Unit, School of Life Sciences, Sambalpur University, Orissa, India.

'Gudakhu' is a paste-like tobacco preparation used widely in Orissa and neighbouring states of India. During use it is rubbed over the teeth and gum with a finger tip. Besides

tobacco, it contains molasses, lime, red soil and water. The genotoxic potential of acetone extract of gudakhu was evaluated in mice in vivo using the chromosome aberration assay, micronucleus test and SCE analysis following single as well as long-term repeated treatment. The animals received an aqueous suspension of the extract via the oral route. Gudakhu extract induced significantly high frequencies, compared to controls, of chromosome aberrations, micronuclei (MN) and SCEs. Single treatment with different doses clearly revealed a distinct dose-dependent increase of the effects in all the assays. Analysis of MN in regenerated hepatocytes also indicated a significant positive correlation between time-course of chronic treatment and frequencies of micronucleated cells. But incidences of chromosome aberrations, MN and SCEs in bone marrow cells following repeated treatment for different periods did not differ greatly from each other; and these repeated treatment data, particularly in the MNT in bone marrow cells and the SCE assay, also did not differ markedly from the respective single treatment data for the same dose. This was probably due to the proliferative nature of the bone marrow cells.

144. Das RK, Dash BC

Genotoxicity of 'gudakhu', a tobacco preparation. II. In habitual users

Food Chem Toxicol. 1992 Dec;30(12):1045-9.

Environmental Mutagenesis Unit, School of Life Sciences, Sambalpur University, Orissa, India.

The genotoxic potential of 'gudakhu', a paste-like tobacco preparation that is used widely in Orissa, India, was evaluated using the micronucleus test in exfoliated cells of the buccal mucosa. Cells from 120 habitual users and from 102 non-users were examined. The incidence of micronuclei (MN) was increased in the mucosa cells of users, and the increase was significant in those who had used gudakhu for more than 5 yr. The increased incidence of MN was significantly correlated with the period of use of gudakhu, as well as with the frequency of daily use. There were no significant differences between the results for men and women.

145. Gupta PC, Mehta FS, Pindborg JJ, Bhonsle RB, Murti PR, Daftary DK, Aghi MB

Primary prevention trial of oral cancer in india: a 10-year follow-up study

J Oral Pathol Med. 1992 Nov;21(10):433-9.

Basic Dental Research Unit, Tata Institute of Fundamental Research, Bombay, India.

Oral cancer is caused by chewing and smoking of tobacco. To assess the feasibility of primary prevention of oral cancer, two cohorts were studied in base-line surveys and then followed up annually for 10-yr in Ernakulam district of Kerala state. The

intervention cohort consisted of 12212 tobacco users aged 15 yr and over, who were exposed to a concentrated program of education against tobacco use. The control cohort was a non-concurrent cohort of 6075 tobacco users studied using similar methods but with a minimal amount of advice against tobacco use. The stoppage of tobacco use increased and the incidence rate of leukoplakia decreased significantly and substantially in the intervention cohort compared to the control cohort. The decrease in the incidence of leukoplakia was indicative of the decrease in the risk of oral cancer since the two were intimately related. This study demonstrated feasibility of primary prevention of oral cancer.

146. Jaju RJ, Patel RK, Bakshi SR, Trivedi AH, Dave BJ, Adhvaryu SG.

Chromosome damaging effects of pan masala.

Cancer Lett. 1992 Aug 31;65(3):221-6.

Cell Biology Division, Gujarat Cancer and Research Institute, Ahmedabad, India.

Effects of aqueous extracts of a popular brand of pan masala with and without tobacco (PM-T and PM) were studied for short duration treatment employing an in vitro system. Metabolic activation with S9 mix was also included. Frequency of all the three cytogenetic endpoints viz., chromosome aberration (CA); sister chromatid exchange (SCE) and % micronucleated cells (% MNC) were found to be elevated significantly in a dose-dependent manner in cultures without metabolic activation. However, addition of S9 activation system resulted in suppression of chromosomal damage. Our findings indicate that pan masalas contain water soluble direct acting mutagens.

147. Sarma AB, Chakrabarti J, Chakrabarti A, Banerjee TS, Roy D, Mukherjee D, Mukherjee A.

Evaluation of pan masala for toxic effects on liver and other organs.

Food Chem Toxicol. 1992 Feb;30(2):161-3.

Central Drugs Laboratory, Calcutta, India.

The acute and chronic oral toxicity of pan masala (betel quid without betel leaf) was assessed in gavage studies in rats. Clinical parameters (liver and serum glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase and alkaline phosphatase) and organ weights were measured. The results indicate that chronic feeding of pan masala impaired liver function, as indicated by changes in enzyme activity, and decreased relative weights of the gonads and brain.

148. Chakrabarti RN, Dutta K, Sikdar K, Ghosh K

Smokeless tobacco and premalignant and malignant lesions of the oral cavity

Indian J Med Sci. 1991 Oct;45(10):273-5.

The paper compares the prevalence of oral carcinoma and dysplasia in smokeless tobacco users and non users. A total of 3205 subjects were studied. Of the smokeless tobacco users, 1.96 percent had oral carcinoma compared with 0.36 percent of non-users. The prevalence of oral dysplasia in the users' group was 14.4 percent as compared with 6.85 percent in the group of non-users.

149. D. Saranath, S. E. Chang, L. T. Bhoite, R. G. Panchal, I. B. Kerr, A. R. Mehta, N. W. Johnson, M. G. Deo
High frequency mutation in codons 12 and 61 of H-ras oncogene in chewing tobacco-related human oral carcinoma in India

Br J Cancer. 1991 Apr;63(4):573-8.

Cell and Developmental Pathology Division, Cancer Research Institute, Bombay, India.

57 primary tumour samples from Indian oral cancer patients with a 5-15 year tobacco chewing habit, were examined for mutational activation in codons 12, 13 and 61 of the H-ras, K-ras and N-ras oncogenes. The highly sensitive assay based on specific oligonucleotide hybridisation following in vitro amplification of unique sequences by polymerase chain reaction was employed. Mutations were detected in twenty (35%) of the samples and were restricted to H-ras, codons 12, 13 and 61. Two cases had concurrent mutations in codons 12 and 61. The majority of the mutations were at H-ras 61.2 (Glutamine to Arginine) and H-ras 12.2 (Glycine to Valine). Three of the less frequent mutations are apparently novel. Interestingly, eight of the samples with H-ras mutations also showed loss of wild-type H-ras, as judged by absence of signals for wild-type codons 12 or 61 on dot blots. The specific H-ras mutations in these oral malignancies associated with tobacco chewing, may represent an important example of an environmental carcinogen-induced step, in a pathway leading to malignant transformation.

150. Dave BJ, Trivedi AH, Adhvaryu SG.

Cytogenetic studies reveal increased genomic damage among 'pan masala' consumers.

Mutagenesis. 1991 Mar;6(2):159-63.

Cell Biology Division, Gujarat Cancer and Research Institute, Ahmedabad, India.

Pan masala (PM), a dried powdered mixture containing ingredients like areca nut, catechu, lime, cardamom and flavouring agents, is consumed abundantly by Indians and is also exported to Western countries. Pan masala with tobacco (PM-T) is also available on the market. In view of the role of the ingredients of PM in the causation of oral diseases, the possible harmful effects of consuming this complex mixture were analysed

in individuals regularly consuming PM and among healthy non-consuming controls without any habit. Three cytogenetic endpoints and two tissues were employed to assess possible DNA damage. Sister chromatid exchange and chromosome aberrations were estimated in the peripheral blood lymphocytes, tissues indirectly exposed to the substance and the frequency of micronucleated cells was scored in the tissue directly in contact with PM, i.e. the exfoliated buccal mucosa cells. All three cytogenetic endpoints demonstrated a statistically significant increase (P less than 0.001) among the PM consumers as compared with the non-consuming controls.

151. K. Jayant, P. N. Notani, S. S. Gulati, V. V. Gadre

Tobacco usage in school children in Bombay, India. A study of knowledge, attitude and practise

Indian J Cancer. 1991 Sep;28(3):139-47.

Cancer Research Institute, Parel, Bombay, India.

A study of knowledge, attitude and practice with regard to tobacco usage was conducted in 1278 boys and 353 girls studying in the final year in various schools in Bombay. The proportion of boys given to one or the other form of tobacco usage (including experimenters/tryers) was significantly higher in private English median schools (22.5%) compared to private Indian language schools (6.9%) or municipal Indian language schools (13.8%). There was also a significant difference between the two types of Indian schools. Girls from only Indian language schools were entered into the study and the proportion of tobacco users in them was very low (1.1%). Most (86%) boys who used tobacco were smokers. Hence the detailed analysis is restricted to smokers. Several probable factors influencing smoking behavior were studied. It was found that significantly higher proportion of boys smoked if their father or best friend smoked. Generally boys were more sensitive to best friend's or elder brother's disapproval than to parental. They were well informed about harmfulness of smoking but knowledge about specific health hazards was limited. Most of them had a positive attitude towards nonsmoking and smoking control programmes. Tobacco use has been proven to be a major health hazard. Although its use in adults in India is common, prevalence in adolescents in urban schools is not yet high. Before the situation changes we need to mount anti-tobacco educational programmes and work towards a non-tobacco generation to contain the harmful consequences of tobacco usage.

152. Khirme RD, Mehra YN, Mann SB, Mehta SK, Chakraborti RN.

Effect of instant preparation of betel nut (pan masala) on the oral mucosa of albino rats.

Indian J Med Res. 1991 Apr;94:119-24.

Department of Otolaryngology, Postgraduate Institute of Medical Education & Research, Chandigarh.

Paste made out of an instant betel nut preparation was painted into the oral cavity of 21 albino rats on alternate days for a period of six months. Biopsies were taken from the oral mucosa at the beginning of the study and every two months thereafter and compared histopathologically with those obtained from a control group of 14 albino rats. Mild to moderate loss of nuclear polarity and increase in keratoses, parakeratoses, inflammatory cell infiltration and vascularity were noted when compared to the control group. The increase in mitotic figures was statistically insignificant and no definite changes in pigmentation or atypical cells were seen. These findings suggest the possibility of mild leukoplakia. Submucosal collagen increased steeply and steadily throughout the study period and at the end of six months, 88.23 per cent of biopsies showed thickened and condensed sub-mucosal collagen, indicating submucous fibrosis.

153. Mukherjee A, Chakrabarti J, Chakrabarti A, Banerjee T, Sarma A

Effect of 'Pan Masala' on the germ cells of male mice.

Cancer Lett. 1991 Jul 4;58(3):161-5.

Centre for Advanced Study in Cell and Chromosome Research, University of Calcutta, India.

Cytogenetic analyses of meiotic metaphase I germ cells and abnormalities of head morphology of caudal sperms were conducted in male mice following oral feeding of Pan Masala. The substance was ground to a fine powder, dispersed in polysorbate solution and administered via gavage to the animals at 84, 420 and 840 mg/kg body weight at the rate of 10 ml/kg body weight. Polysorbate and cyclophosphamide served as the vehicle control and positive control respectively. The two higher doses, 420 and 840 mg, gave a significant increase in the frequency of X-Y univalents and breaks over those of the vehicle control. Frequency of sperm head abnormalities were significantly high for all the doses tested. The results indicate that Pan Masala is a potent clastogen, reaches the testes and affects the germinal cells.

154. Mukherjee A, Giri AK.

Sister chromatid exchange induced by 'pan masala' (a betel quid ingredient) in male mice in vivo.

Food Chem Toxicol. 1991 Jun;29(6):401-3.

Department of Botany, University of Calcutta, India.

Sister chromatid exchange (SCE) induced in vivo by 'pan masala', a betel quid ingredient, was studied in male mice. The mice were injected ip with an aqueous suspension of pan masala at doses of 5, 12.5, 25, 50, 100 or 200 mg pan masala/kg body weight. A significant dose-related increase in SCE was observed (Cochran-

Armitage trend test). The minimum effective dose was 25 mg/kg. The two highest doses caused significant delays in the cell cycle. These results indicate that pan masala is a potential DNA-damaging agent and cytotoxic to bone marrow cells.

155. S. G. Adhvaryu, B. J. Dave , A. H. Trivedi

Cytogenetic surveillance of tobacco-areca nut (mava) chewers, including patients with oral cancers and premalignant conditions

Mutat Res. 1991 Sep;261(1):41-9.

Department of Cancer Biology, Gujarat Cancer and Research Institute, Ahmedabad, India.

Three cytogenetic endpoints were studied in non-chewing healthy controls and 3 groups of tobacco-areca nut chewers, viz. normal chewers, chewers with oral submucous fibrosis and chewers with oral cancer. Frequencies of sister-chromatid exchanges and chromosome aberrations in peripheral blood lymphocytes and of micronucleated cells in exfoliated buccal mucosa were evaluated. All the parameters showed statistically significant elevations in all 3 groups of chewers compared to the controls. The data indicate possible application of the parameters as sensitive endpoints for monitoring tobacco-areca nut chewers, the group of individuals at higher risk of developing oral cancer, the commonest cancer among Indian males.

156. Bagwe AN, Ganu UK, Gokhale SV, Bhisey RA.

Evaluation of the mutagenicity of 'pan masala', a chewing substitute widely used in India.

Mutat Res. 1990 Aug;241(4):349-54

Genotoxicity Unit, Tata Memorial Centre, Bombay, India.

Mutagenicity of polar and non-polar extracts of a popular brand of 'pan masala' was examined using the Salmonella/mammalian microsome test (Ames assay) and 2 tester strains of Salmonella typhimurium, TA98 and TA100. These extracts were also subjected to pretreatment with sodium nitrite at acidic pH, to simulate conditions for endogenous nitrosation. The aqueous, aqueous:ethanolic and chloroform extracts as well as their nitrosated mixtures were non-mutagenic in the Ames assay, in the presence and absence of metabolic activation. Only the ethanolic extract elicited a weak mutagenic response in strain TA98 without metabolic activation demonstrating the presence of direct-acting frameshift mutagens in 'pan masala'.

157. P. K. Ghosh, R. Madhavi, M. Guntur, R. Ghosh

Sister chromatid exchanges in patients with oral submucous fibrosis

Cancer Genet Cytogenet. 1990 Feb;44(2):197-201.

Department of Anthropology, University of Delhi, India.

The incidence of sister chromatid exchange (SCE) was investigated in the lymphocyte chromosomes of 45 patients with oral submucous fibrosis and 56 age- and sex-matched nonsmoking controls. The frequency of SCE was 9.26 ± 2.15 in patients with oral submucous fibrosis, which was significantly higher than the mean SCE value of 5.49 ± 1.24 observed in normal controls. The frequency of SCE in patients with oral submucous fibrosis addicted to the habit of betel with tobacco chewing, "bidi"/cigarette smoking and combined habits of chewing and smoking of tobacco were 8.12 ± 1.69 , 9.43 ± 1.87 , and 10.06 ± 2.28 , respectively. These values were also significantly higher as compared with the SCE values observed in normal controls.

158. P. N. Sinor, P. C. Gupta, P. R. Murti, R. B. Bhonsle, D. K. Daftary, F. S. Mehta, J. J. Pindborg

A case-control study of oral submucous fibrosis with special reference to the etiologic role of areca nut

J Oral Pathol Med. 1990 Feb;19(2):94-8.

Basic Dental Research Unit, Tata Institute of Fundamental Research, Bombay, India.

A case-control study to elucidate the etiology of oral submucous fibrosis was conducted in Bhavnagar, Gujarat. Sixty consecutively arriving oral submucous fibrosis patients at a dental clinic were selected as cases. An equal number of controls matched for age, sex, religion and socioeconomic status were selected from individuals who did not exhibit any oral mucosal lesion or condition. Among cases, 98% chewed areca nut regularly in one form or the other whereas among controls 35% chewed areca nut, giving an overall relative risk of 109.6. Areca nut chewing was practiced most commonly in the form of mawa: a mixture containing mainly areca nut (over 90% by weight), some tobacco, and a few drops of lime. Mawa chewers and those who chewed mawa along with other chewing habits showed very high relative risks. The relative risks increased with increase in the frequency as well as the duration of chewing habits. In a bivariate analysis the effect of frequency and duration of chewing appeared to be multiplicative. The present findings confirm areca nut as the most important etiologic factor in oral submucous fibrosis.

159. P. S. Gijare, K. V. Rao, S. V. Bhide

Modulatory effects of snuff, retinoic acid, and beta-carotene on DMBA-induced hamster cheek pouch carcinogenesis in relation to keratin expression

Nutr Cancer. 1990;14(3-4):253-9.

Carcinogenesis Division, Tata Memorial Centre, Parel, Bombay, India.

The hamster cheek pouch (HCP) serves as an excellent model system not only for the studies on initiation and promotion but also for the modulation of experimental oral carcinogenesis. In our studies, HCPs treated with 7,12-dimethylbenz[a]anthracene (DMBA) showed both cheek pouch and stomach papillomas. Utilizing this model system, we tested and compared the modulatory effects of snuff, retinoic acid, and beta-carotene on the incidence of tumors and the keratin expression pattern. HCPs treated with snuff, either alone or in combination with DMBA, resulted in stomach papillomas. HCPs treated with snuff showed no cheek pouch tumors, and those treated with snuff and DMBA showed only 10-15% tumor incidence. Both beta-carotene and retinoic acid showed a total inhibition of DMBA-induced carcinogenesis in the HCP as well as in the stomach. The keratin expression pattern showed alterations depending on the experimental conditions.

160. P. S. Gijare, K. V. Rao, S. V. Bhide

Inhibitory effects of snuff extract on ornithine decarboxylase and aryl hydrocarbon hydroxylase activities in relation to cell proliferation of mouse tongue epithelial cells

Indian J Exp Biol. 1990 Nov;28(11):1012-6.

Carcinogenesis Division, Tata Memorial Centre, Bombay, India.

Effect of snuff extract (SE) on cell proliferation as measured by 3H thymidine (TdR) uptake, induction of ornithine decarboxylase (ODC) and aryl hydrocarbon hydroxylase (AHH) was studied in primary embryonal mouse tongue cultures. Cultures treated with SE in combination with 7,12-dimethylbenz(a)anthracene (DMBA) showed inhibition of cell proliferation and decrease of ODC and AHH activities, compared to control, DMBA, and DMBA + 12-O-tetradecanoylphorbol 13-acetate treated cultures.

161. R. Sankaranarayanan

Oral cancer in India: an epidemiologic and clinical review

Oral Surg Oral Med Oral Pathol. 1990 Mar;69(3):325-30.

Regional Cancer Centre, Kerala, India.

This article reviews the epidemiologic and clinical aspects of oral cancer in India, where the disease ranks number one among all cancers in male patients and number three among cancers in female patients. Causal association between oral cancer and the chewing of betel quids containing tobacco leaves or stem and other tobacco habits has been extensively studied. But there is need for more in-depth studies on the role of alcohol, diet, and oral hygiene practices in India. The exciting

opportunity provided by the well-established oral precancerous lesions for intervention and early detection programs is also discussed. The peak age frequency of occurrence is at least a decade earlier than that described in Western literature. Sex ratio reveals a 2:1 preponderance of male patients. Only 10% to 15% of cases present in localized stages. The poor survival revealed by existing studies is mainly due to the overwhelming proportion of advanced cases. The excellent opportunity for more research and efforts in prevention and control of oral cancer in India is highlighted in this review.

162. Adhvaryu SG, Dave BJ, Trivedi AH.

An in vitro assessment of the genotoxic potential of pan masalas.

Indian J Med Res. 1989 Apr;90:131-4.

An aqueous extract of pan masala was tested for its in vitro effects on Chinese hamster ovary (CHO) cells by utilizing parameters like sister chromatid exchange (SCE), cellular kinetics and chromosome aberration (CA) assay. The cytogenetic damage brought about by the extract was dose dependent. The increase in SCE values was highly significant (P less than 0.001) for all the three concentrations tested. The treatment delayed the cell cycle progression. Frequencies of chromosome aberrations were elevated for all the concentrations utilized, however, a significant rise was obtained only at the highest concentration of 50 microliters/ml.

163. D. N. Rao, L. D. Sanghvi, P. B. Desai

Epidemiology of esophageal cancer

Semin Surg Oncol. 1989;5(5):351-4.

Department of Medical Records and Statistics, Tata Memorial Hospital, Bombay, India.

The incidence of cancer of the oesophagus is high in India but not as high as the rates reported from the Caspian Littoral of Iran. Incidence data available for three places in India--Bombay, Madras, and Bangalore--show regional variations. In Bombay, the rates for males are high compared to Madras and Bangalore. A case control study of 503 oesophageal cancer cases in males and 634 controls registered at the Tata Memorial Hospital during the period 1980-84 was carried out to determine the association of oesophageal cancer with two types of dietary practices, viz., vegetarian and non-vegetarian, in addition to tobacco and alcohol habits. In the presence of an alcohol habit, the relative risk for tobacco chewing and smoking was observed to be high in the non-vegetarian group compared to the vegetarian group. A vegetarian diet was protective. Further studies are suggested to confirm this finding.

164. P. C. Gupta, R. B. Bhonsle, P. R. Murti, D. K. Daftary, F. S. Mehta, J. J. Pindborg
An epidemiologic assessment of cancer risk in oral precancerous lesions in India with special reference to nodular leukoplakia
Cancer. 1989 Jun 1;63(11):2247-52.
Basic Dental Research Unit, Tata Institute of Fundamental Research, Bombay, India.

A cohort of 12,212 tobacco users was followed up annually to assess malignant potential of oral precancerous lesions in the Ernakulam district in Kerala, India. A total of 19 new oral cancers were diagnosed over a period of 8 years, and 15 (79%) of these arose from some preexisting precancerous lesion or condition. Nodular leukoplakia showed highest rate of malignant transformation (16% per year) as six of 13 nodular leukoplakia underwent malignant transformation over a mean follow-up period of 2.8 years. The relative risk (3243.2) compared with individuals with tobacco habits but without any precancerous oral lesion was also the highest for nodular leukoplakia. In addition, nodular leukoplakia was associated with submucous fibrosis in two patients, which progressed to oral cancer and was the clinical diagnosis for four lesions that turned out to be malignant on histopathologic examination. Nodular appearance was noted in two other precursor lesions as well. Thus, 14 of 19 oral cancers (74%) were either preceded by nodular leukoplakia and with lesions showing a distinct nodular appearance, or had the clinical appearance of nodular leukoplakia.

165. P. R. Padma, V. S. Lalitha, A. J. Amonkar, S. V. Bhide
Anticarcinogenic effect of betel leaf extract against tobacco carcinogens
Cancer Lett. 1989 Jun;45(3):195-202.
Carcinogenesis Division, Cancer Research Institute, Tata Memorial Centre, Bombay, India.

Epidemiological studies have implicated that betel quid offers some protection to tobacco induced carcinogenesis. Earlier studies in our laboratory have shown betel leaf extract (BLE) to be antimutagenic against standard mutagens and tobacco-specific N'-nitrosamines (TSNA), N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). In the present study, we have tested the anticarcinogenic effect of BLE using Swiss male mice. Two protocols of study were used to test this effect. In the first protocol, the effect of BLE was tested against the standard carcinogen benzo[a]pyrene (BP) using Wattenberg's stomach tumor model. In this protocol, BLE inhibited the tumorigenicity of BP to a significant extent. In the second protocol, the effect of BLE against the two tobacco-specific nitrosamines, NNN and NNK was studied using long-term studies on Swiss male

mice. The nitrosamines were administered on the tongues of the mice, while the BLE was supplied in drinking water. Two doses of NNN (22 mg and 72 mg) and one dose of NNK (22 mg) were used. In this study, it was observed that the number of tumor bearing animals decreased, but the difference was significant only in the group treated with the low dose of NNN in combination with BLE. However, in all the BLE treated animals, irrespective of the dose of nitrosamine, the hepatic vitamin A and C levels were elevated significantly as compared to the corresponding nitrosamine-treated controls. These results indicate that BLE has a promising anticarcinogenic role to play in tobacco induced cancer.

166. R. Sankaranarayanan, S. W. Duffy, G. Padmakumary, N. E. Day, T. K. Padmanabhan
Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India
Br J Cancer. 1989 Oct;60(4):638-43.
Regional Cancer Centre, Trivandrum, India.

A case-control study of cancer of the gingiva was carried out in Kerala, Southern India, using 187 cases and 895 hospital-based controls. We investigated the effects on risk in males of pan (betel)-tobacco chewing, bidi and cigarette smoking, drinking alcohol and taking snuff. In females only pan-tobacco chewing was investigated as very few females indulged in the other habits. Among males, significant positive associations with risk were observed for pan-tobacco chewing ($P < 0.001$), bidi smoking ($P < 0.001$) alcohol drinking ($P < 0.001$) and snuff use ($P < 0.05$). In females, pan-tobacco chewing had a similar predisposing effect ($P < 0.001$). Daily frequency of pan-tobacco chewing was the strongest predictor of risk in males, with a relative risk of 15.07 associated with chewing ten or more quids per day. The corresponding relative risk among females was 13.69. In males a relative risk of 3.20 was associated with smoking more than 20 bidis per day, and relative risks of 2.62 and 3.90 were associated with regular use of alcohol and snuff respectively. Surprisingly high relative risks were observed in association with occasional use of pan-tobacco, bidi, cigarettes, alcohol and snuff. A stepwise logistic regression analysis yielded four predictors: pan-tobacco daily frequency, duration of bidi use, and alcohol and snuff use (regular versus never). There were also significantly elevated risks associated with occasional indulgence in these four habits. Total lifetime exposure was no better at predicting risk than daily frequency or duration of habits.

167. P. K. Nanda, M. M. Sharma

Immediate effect of tobacco chewing in the form of 'paan' on certain cardio-respiratory parameters

Indian J Physiol Pharmacol. 1988 Apr-Jun;32(2):105-13.

Department of Physiology, Indira Gandhi Medical College, Shimla.

Immediate effect of tobacco in the form of chewing was evaluated in 40 healthy males (mean age 26.27 yrs.) not habituated to tobacco, who were given paan containing 200 mg of tobacco to chew (group T). Heart rate (HR), blood pressure (BP), forced vital capacity (FVC), FEV1 and peak expiratory flow rate (PEFR) were measured twice for each subject, once before chewing and again immediately after completion of chewing. Another 24 age and sex matched controls (group C) were given paan without tobacco to chew and cardiorespiratory parameters were recorded as for group T subjects. Electrocardiography was recorded in 10 group T and 10 group C subjects. Effect of tobacco chewing was also evaluated in 10 habitual tobacco chewers. Results showed statistically significant increments in HR and BP as well as a decline in T wave amplitude in ECG following tobacco chewing (group T subjects). The changes in HR and BP lasted for 15-30 mins, as observed in 10 of group T subjects. The FVC, FEV1 and PEFR showed marginal, though non-significant, increments after tobacco chewing. No significant difference in the cardiorespiratory responses to tobacco chewing could be seen between habitual and nonhabitual (group T) tobacco chewers. The changes in cardiovascular and respiratory parameters following paan (without tobacco) chewing in the control subjects were negligible and nonsignificant.

168. R. Ghosh, J. K. Sharma, P. K. Ghosh

Sister chromatid exchanges in the lymphocytes of patients with oral leukoplakia

Cancer Genet Cytogenet. 1988 Dec;36(2):177-82.

Department of Anthropology, University of Delhi, India.

The incidence of sister chromatid exchange (SCE) was investigated in lymphocyte chromosomes of 59 patients with oral leukoplakia and 65 age- and sex-matched nonsmoking controls. The frequency of SCE was found to be 8.61 ± 1.89 in patients with oral leukoplakia, which was significantly higher than the mean SCE value of 5.58 ± 1.26 observed in normal controls. The frequency of SCE in patients with oral leukoplakia addicted to the single habit of betel with tobacco chewing, bidi/cigarette smoking, and combined habits of chewing and smoking of tobacco were found to be 7.95 ± 1.63 , 8.17 ± 1.66 , and 9.23 ± 2.14 , respectively. These values were also significantly higher as compared to the SCE values observed in normal controls.

169. R. K. Dikshit, J. G. Buch, S. M. Mansuri

Effect of tobacco consumption on semen quality of a population of hypofertile males

Fertil Steril. 1987 Aug;48(2):334-6.

Effect of tobacco use (by chewing or smoking) on semen quality has been seen. Semen analysis of 119 tobacco chewers and 219 smokers was compared with those of 288 control patients. Some decrease in the ejaculate volume, sperm density, and total count was observed in tobacco users, but it was statistically insignificant. No difference was found in other parameters, like motility and morphology. It is concluded that tobacco use by chewing or smoking is not associated with impaired semen quality in males selected from an idiopathically hypofertile population.

170. P. C. Gupta, F. S. Mehta, J. J. Pindborg, M. B. Aghi, R. B. Bhonsle, D. K. Daftary, P. R. Murti, H. T. Shah, P. N. Sinor

Intervention study for primary prevention of oral cancer among 36 000 Indian tobacco users

Lancet. 1986 May 31;1(8492):1235-9.

In a house-to-house survey, 36 471 tobacco chewers and smokers were selected from the rural population in three areas of India. These individuals were interviewed for their tobacco habits and examined for the presence of oral leukoplakia and other precancerous lesions, first in a baseline survey, and then annually over a 5-year period. By personal advice and via the mass media they were encouraged to give up their tobacco habits. The follow-up rate was 97%. The control cohort was provided by the first 5-year results from a 10-year follow-up study conducted earlier in the same areas with the same methodology but on different individuals without any educational intervention. In Ernakulam district (Kerala) and Srikakulam district (Andhra) substantially more people stopped their tobacco habit and reduced the frequency of tobacco use in the intervention cohort than in the control cohort; in Bhavnagar district (Gujarat) the intervention group showed only a slightly higher proportion stopping their tobacco habits and no difference in the proportion reducing them. The 5-year age-adjusted incidence rate of leukoplakia in Ernakulam district was 11.4 in the intervention group versus 47.8 among men, and 5.8 versus 33.0 among women; and for palatal lesions in Srikakulam district the corresponding figures were 59.8 versus 260.8 among men and 289.5 versus 489.5 among women. In Bhavnagar the incidence rate of leukoplakia did not differ between the cohorts. Since most oral cancers are preceded by precancerous lesions, education on tobacco habits should be a feasible and effective approach to primary prevention of oral cancer.

171. P. C. Gupta, M. B. Aghi, R. B. Bhonsle, P. R. Murti, F. S. Mehta, C. R. Mehta, J. J. Pindborg
An intervention study of tobacco chewing and smoking habits for primary prevention of oral cancer among 12,212 Indian villagers
IARC Sci Publ. 1986;(74):307-18.

In a house-to-house screening survey, 12,212 tobacco chewers and smokers were selected from the rural population in the Ernakulam district, Kerala state, India. These individuals were interviewed for their tobacco habits and examined for the presence of oral cancer and precancerous lesions, first in a baseline survey, and then annually, over a five-year period. They were educated using personal and mass media communication to give up their tobacco habits. The control group was provided from the results of the first five years of a 10-year follow-up study conducted earlier by the authors in the same area with the same methodology but on different individuals without any educational intervention. The stoppage of the tobacco habit was substantially higher in the intervention group (9.4%) compared to the control group (3.2%). A logistic regression analysis showed that the behavioural intervention was helpful to all categories of individuals, however, the effect was different for different categories: intervention was more helpful to men, chewers, and those with a long duration of the habit. These individuals rarely quit their habit without intervention.

172. P. R. Murti, D. K. Daftary, R. B. Bhonsle, P. C. Gupta, F. S. Mehta, J. J. Pindborg
Malignant potential of oral lichen planus: observations in 722 patients from India
J Oral Pathol. 1986 Feb;15(2):71-7.

The malignant potential of oral lichen planus was assessed on the basis of observations in 722 patients found among 27,599 individuals examined in various epidemiologic studies in Kerala, Ernakulam district, India. 702 patients with oral lichen planus were re-examined annually over a 10-year period with a mean observation period of 5.1 years. Most of the lesions (93%) were observed among tobacco users. Carcinoma developed in 3 (0.4%) patients with oral lichen planus. Clinically, all 3 had atrophic components in their lesions, and all were tobacco users. The relative risk of a lichen planus developing oral cancer compared to a tobacco user was estimated as 3.3. However, this relative risk was not significant. Histologically, 74% of the 94 biopsies from oral lichen planus showed epithelial atrophy. Two of the 3 in whom cancer developed also showed epithelial atrophy. It is felt that epithelial atrophy probably renders the mucosa more vulnerable to the carcinogenic action of tobacco. Although this study could not confirm the precancerous nature of this disease with a high degree of certainty, the disease did not appear to be innocuous either.

ABSTRACT NOT AVAILABLE

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