RESEARCH ARTICLE

Relationship of Lifetime Exposure to Tobacco, Alcohol and Second Hand Tobacco Smoke with Upper aero-digestive tract cancers in India: a Case-Control Study with a Life-Course Perspective

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Abstract

Background: Squamous cell carcinomas of the upper aero-digestive tract (UADTSCC) are a multifaceted public health problem. Effects of lifestyle risk factors, including tobacco (chewing and smoking), alcohol drinking and exposure to second hand tobacco smoke (SHS) at home and their association with UADT cancers was assessed in a case-control study with a life-course perspective. The study was conducted at two different hospitals in Pune, India. **Material and methods:** The total sample size (N=480) included 240 histopathologically confirmed cases of UADT cancers and an equal number of controls frequency matched with cases by gender and age distribution (+5 years). All the patients were interviewed face-face using structured questionnaires. Self-reported information on socio-demographic and lifestyle risk factors from childhood to the date of diagnosis of disease/cancer was obtained. Frequency, duration and age of initiation of habits were also recorded to study dose-response relationships. Odds ratios and their 95% confidence intervals were calculated through unconditional logistic regression, adjusting for relevant potential confounders. **Results:** Chewing tobacco emerged as the strongest predictor for UADT cancers (OR=7.61; 95% CI 4.65-12.45) in comparison to smoking and drinking alcohol. Exposure to SHS during childhood (<16 years) rather than ≥16 years increased the risk (OR=4.05; 95% CI 2.06-7.95). Combined effects of tobacco and alcohol consumption habits elevated the risk by twelve fold (OR=12.05; 95% 4.61-31.49) in comparison to never users of these habits. Furthermore, the combination of these lifestyle risk factors accounted for 86.8% of population attributable risk. **Conclusions:** Early exposure to various modifiable lifestyle risk factors has a strong positive association with UADT cancer incidence. Effective future public health interventions with focus on vital time points in life targeting these risk factors could possibly be a major step in primary prevention and control of this cancer at the population level.

Keywords: Upper aero-digestive tract cancer- chewing tobacco- smoking- alcohol- second hand tobacco smoke

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Introduction

Cancers of the upper aero-digestive tract (UADT: oral cavity, pharynx, larynx and oesophagus) are a leading cause of mortality and morbidity with an estimated 725,000 deaths and 1,055,000 new cases worldwide, ranking as the fifth commonest cancer (Gupta et al., 2016, Gupta and Kumar 2016). Though the actual aetiology of UADT cancers is multi-factorial, extensive research has demonstrated that tobacco consumption in all its forms and alcohol drinking are prominent modifiable risk factors (Gupta and Johnson, 2014). Large variations in incidence of UADT cancers are observed globally. South-East Asia, including India, is the most severely affected region in view of wide prevalence of these lifestyle risk factors.

Diagnosis of UADT cancers occurs at the final conclusion of progressive aggregation of genetic alterations in a long complex pathological process which had developed roots decades ago. Traditional studies allow the understanding of various risk factors at the stage of life when the study was conducted. Application of a life-course model would demonstrate the influence of these risk factors at various stages of life on incidence of UADT cancers (Gupta et al., 2015). Growing scientific evidence connotes that there are critical and sensitive developmental stages in childhood, adolescence and adulthood when environmental exposures influence the life-course trajectories with health implications in later stages of life (Gupta et al., 2015). Adult exposure to habits of tobacco consumption as well as alcohol drinking has been studied in detail for various UADT cancers. However, the independent interactive and qualitatively different exposure time interactions which these risk factors may have over a life-course leading to UADT cancers, including exposure to SHS, is a relatively neglected sphere of research.

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Exploring the risk posed by these lifestyle habits over the life-course of an individual suffering from UADT cancers, potential importance of timing of initiation and duration of exposure can probably be established. Confirming the aetiological role of risk factors over life-course will enable development of primary prevention strategies at early life-time points, focusing on at risk vulnerable population groups. At present, there are no established population based screening strategies in use to enable early diagnosis of UADT cancers. In such a scenario, primary prevention acting against such identified risk factors can possibly be an effective way to reduce the burden of disease as well as mortality due to these cancers.

We conducted this study with the objective of relating early life exposures as well as recent information about tobacco consumption, exposure to SHS at home and alcohol drinking and their association with UADT cancers among adult residents of Pune city, Maharashtra, India.

Material and methods

Study patients

This is a hospital based case-control study. Patients ranging in age group from 30-80 years were enrolled from two different multidisciplinary hospitals: Sadhu Vaswani Mission's Medical Complex and Command Hospital in Pune, Maharashtra, India between June 2014 to May 2015. Both the study hospitals are located at a distance of around two kms apart from each other and well connected by public means of transport. As both the hospitals are close to each other, they share the same population source and are truly representative of the general population of Maharashtra. Furthermore, both the hospitals are multi-disciplinary general hospitals equipped with modern amenities and diagnostic aids designed and planned to ensure a close co-ordination between all disciplines and departments, thus ensuring that the patients receives comprehensive cancer care.

A total of 242 incident cases with histopathologically confirmed diagnosis of UADTSCC were enrolled for the study. Only two patients refused to complete the study due to ill health and inability to speak. Incident cancer cases were those who were diagnosed within past two months from the date of interview. The date of diagnosis of cancer cases was available from the hospital records. Cases were enrolled in the study irrespective of their gender, age and stage of cancer. The UADT cancer sub-sites were coded by International Classification of Diseases (ICD-10 codes) (World Health Organization, 2015). These included lip and oral cavity (ICD C00-06), oropharynx (ICD C09-C10), hypopharynx (ICD C13), larynx (ICD C32) and upper third of oesophagus (ICD C15.3) (Slootweg and Eveson, 2005).

A total of 240 controls were also enrolled for the study. None of the controls refused to participate. Control group consisted of randomly selected patients diagnosed with a disease other than UADT cancers who were reporting for non-malignant conditions during the same period, based on "incidence density" sampling (Vandenbroucke and Pearce, 2012). Controls were frequency matched to cases by gender and age within ±5years. They were identified and approached as indoor/outpatients from several hospital departments like orthopaedics, trauma, eye diseases, obstetrics and nephrology clinics from the same study site as cases (Rothman, 2012). Patients diagnosed with diseases related to tobacco and alcohol (e.g. chronic bronchitis, cardiovascular diseases, liver cirrhosis and pancreatitis) or with a previous history of any UADT cancer sub-site were not approached as controls. The exclusion criterion for the cases and controls was their inability to provide consent in presence of witness to participate in the interviews.

Ethical approval

This research was approved by Griffith University Human Research Ethics Committee (Reference No: DOH/10/14/HREC) and by both the participating hospitals in India. Verbal informed consent was obtained from each patient in the presence of a witness.

Data Collection

All the participants were administered a standardized closed ended risk factor questionnaire along with a life-grid in an approximately 30-min face to face interview by the primary author (BG) of this manuscript. Life-grid is an interview tool used to visualize life-course data and to improve the reliability of retrospective data in a case-control study (Berney and Blane, 2003). Both the cases and controls were interviewed at a time of their convenience. The questionnaire contained data on socio-demographic characteristics, life-time exposure history of tobacco in smoking and chewing forms, alcohol drinking and SHS. A life-course approach to the study was given by stratifying the data on risk factors based on age at initiation (years), frequency of exposure (numbers per day) and duration of use in years.

Self-reported lifestyle habits by patients were broadly classified as 'present' or 'past' or 'never'. As there were negligible respondents in the past category, they were combined with the present and recoded as 'ever' category. Patients who smoked or chewed tobacco at least once a day for a minimum of six months prior to the diagnosis of cancer were recorded as 'ever' smokers or chewers. Alcohol drinkers were defined as subjects who drank alcoholic beverages at least once a week for a minimum of six months. Similarly, respondents exposed to SHS at home were defined as 'ever'. Those who abstained from/had no exposure to these habits in their lifetime were defined as 'never'.

Smokers generally smoked tobacco as bidis or cigarettes. Bidis are described as unfiltered cigarettes, hand-rolled dried temburni leaf (Diospyros elanoxylon) with about 0.5 gram of coarse tobacco. In India, one bidi is considered as analogue for one cigarette. SHS is a mixture of exhaled mainstream and side stream smoke released from a smouldering cigarette or bidi amalgamated with the environment air (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004). Tobacco was chewed in isolation or in combination by the 'ever' patients. The most common types of tobacco chewed were gutkha, khaini, mishri, pan masala and/or paan. Western-type spirits like gin, rum, whisky and

brandy (alcohol content more than 40%) were more popular among the 'ever' respondents in comparison to 'toddy' (a locally fermented distilled sap from palm trees) (Lal et al., 2001).

Statistical analysis

The study questionnaire was designed by BG using an online research data collection tool 'Lime Survey' and data was collected using a hand held tablet (Klieve et al., 2010). The data was further compiled in the Statistical Package for Social Sciences (version 22, II, USA) and quality checks were carried out. Categorical demographical variables of cases and controls were compared using the chi-square test. The effect of risk factors on incidence of UADT cancers was estimated with odds ratio (OR) and their corresponding 95% confidence interval (CI), derived from unconditional logistic regression analysis (Breslow and Day, 1980). All the ORs were statistically adjusted for variables like age (continuous), education, family income per month, chewing and smoking tobacco and alcohol (never/ever category). The Hosmer-Lemeshow goodness of fit index has been used to assess the overall model fit. The chi-square for linear trend was calculated when there were more than two levels of exposure using OpenEpi software. StatsDirect statistical software was used to calculate the population attributable risk for each lifestyle habit and combined effects of these habits were obtained using adjusted OR estimates from unconditional logistic regression models. OR estimates for a combination of two habits were obtained after adjusting for the third habit. As there were only two females who self-reported smoking and drinking alcohol, assessment for these two

Table 1. Selected Characteristics of Cases and Controls

Variable name	Cases N (%)	Controls N (%)	P-value
Gender			
Females	79 (32.9)	79 (32.9)	1
Males	161 (67.1)	161 (67.1)	
Anatomical sub-site			
Lip and oral cavity [C00-C06]	187 (77.9)	-	
Oro and hypopharynx [C10 &13]	21 (8.8)	-	
Larynx [C32]	17 (7.1)	-	
Oesophagus [C15.3]	15 (6.3)	-	
Age group (years)			
<40	17 (7.1)	17 (7.1)	0.112
40-49	54 (22.5)	37 (15.4)	
50-59	60 (25.0)	53 (22.1)	
≥60	109 (45.4)	133 (55.4)	
Residence			
Urban	99 (41.3)	122 (50.8)	0.035
Rural	141 (58.8)	118 (49.2)	
Religion			
Muslims	26 (10.8)	31 (12.9)	0.48
Hindu and others	214 (89.2)	209 (87.1)	
Marital status			
Unmarried/widow or widower	18 (7.5)	8 (3.3)	0.044
Currently married	222 (92.5)	232 (96.7)	
Education of study subject			
More than high school	59 (24.6)	42 (17.5)	<0.001
High school	106 (44.2)	152 (63.3)	
Illiterate	75 (31.3)	46 (19.2)	
Employment			
Homemaker	33 (13.8)	47 (19.6)	0.028
Self employed	34 (14.2)	49 (20.4)	
Salaried workers	85 (35.4)	80 (33.3)	
Farmers	88 (36.7)	64 (26.7)	
Family income per month (rupees)			
≥15,000	146 (60.8)	188 (78.3)	<0.001
<15,000	94 (39.2)	52 (21.7)	

P-value was from Pearson's chi-square test; P-value <0.05 is significant

Table 2. Adjusted Odds Ratios and Corresponding 95% Confidence Intervals for UADT Cancers by Chewing Tobacco

Variable name	Cases N (%)	Controls N (%)	Adjusted OR[a] (95% CI)	P-value	P for linear trend
Chewing tobacco					
Never chewers	32 (13.3)	121 (50.4)	1	<0.001	
Ever chewers	208 (86.7)	119 (49.6)	7.61 (4.65-12.45)		
Age at initiation of chewing tobacco (years)					
Never	32 (13.3)	121 (50.4)	1		
>20 (Adulthood)	26 (10.8)	46 (19.2)	2.23 (1.15-4.33)	<0.001	<0.001
16-20 (Adolescence)	120 (50.0)	48 (20.0)	11.48 (5.98-22.05)		
1-15 (Childhood)	62 (25.8)	25 (10.4)	11.70 (6.61-20.72)		
Duration of chewing (years)					
Never	31 (13.0)	121 (50.4)	1	<0.001	<0.001
≤10	19 (7.9)	12 (5.0)	4.76 (2.24-10.14)		
11-20	31 (13.0)	21 (8.8)	5.26 (2.17-12.74)		
21-30	55 (23.0)	30(12.5)	7.58 (4.02-14.27)		
31-40	43 (18.0)	25 (10.4)	8.37 (4.25-16.49)		
> 40	60 (25.1)	31 (12.9)	10.51 (5.44-20.30)		
Frequency of tobacco chewing per day (number)					
Never	32 (13.3)	121 (50.4)	1	<0.001	<0.001
1-5	46 (19.2)	79 (32.9)	2.27 (1.27-4.08)		
6-10	47 (19.6)	26 (10.8)	8.11 (4.16-15.80)		
>10	115 (47.9)	14 (5.8)	36.56 (17.84-74.92)		
Retention time of tobacco in mouth (minutes)					
Never	32 (13.3)	121 (50.4)	1	<0.001	<0.001
1-30	23 (9.6)	91 (37.9)	1.13 (0.61-2.09)		
31-60	30 (12.5)	15 (6.3)	7.55 (3.53-16.16)		
>60	155 (64.6)	13 (5.4)	45.26 (22.47-91.18)		
Site of mouth retention					
Never chewers	32 (13.3)	121 (50.4)	1	<0.001	<0.001
Chewers/no retention	85 (35.4)	73 (30.4)	4.94 (2.86-8.51)		
Between lower lip and lower teeth	35 (14.6)	15 (6.3)	10.42 (4.84-24.43)		
Buccal mucosa	88 (36.7)	31 (12.9)	13.33 (7.21-24.64)		

[a]Adjusted for age (continuous); education; income; smoking tobacco and alcohol drinking habits; 1 indicates reference category

habits in the statistical analysis was restricted to only males. Cumulative years of smoking were calculated as number of bidis/cigarettes smoked in lifetime*duration of smoking in years.

Results

Characteristics of cases and controls

A total of 480 (67.1% males and 32.9% females) patients participated in the study. The mean age (± standard deviation) at diagnosis for UADT cancer cases and controls in the study was 56.35 ± 11.64 and 58.23 ± 10.32 years respectively (P=0.062). The overall interview response rate was 98%. Controls were predominantly patients with diseases of musculoskeletal system and connective tissue disorders (S00-T98 and M00-M99)-37.9%, eye and adnexa (H00-H59)-35%, respiratory system (J00-J99)-25.8% and disorders of skin appendages-1.3%. The disparities among the case and control group regarding the area of residence, religion, marital status, education, employment and family income per month are summarized in Table 1.

Chewing tobacco

In Table 2, compared to 86.7% of the cases, 49.6% of controls were ever chewers. Chewing tobacco in any form showed almost eight-fold increase in risk versus never chewers (OR=7.61; 95% CI 4.65-12.45). There is a clear linear dose-response relationship (for trend, P<0.001 each) between chewing tobacco and risk of UADT cancers in terms of age at initiation (1-15 years, OR=11.70; 95% CI 6.61-20.72), duration (>40 years, OR= 10.51; 95% CI 5.44-20.30), daily frequency (>10 times in a day, OR= 36.56; 95% CI 17.84-74.92) and its retention time in the mouth (>60 minutes, OR=45.26; CI 22.47-91.18). Furthermore, retention of chewing tobacco particularly in buccal mucosa elevated the risk of cancer by more than thirteen folds (OR=13.33; 95% CI 7.21-24.64).

Table 3. Adjusted Odds Ratios and Corresponding 95% Confidence Intervals for UADT Cancers in Males by Smoking Tobacco

Variable name	Cases N (%)	Controls N (%)	Adjusted OR[a] (95%CI)	P-value	P for linear trend
Smoking habit					
Never smokers	92 (57.1)	124 (77.0)	1	<0.001	
Ever smokers	69 (42.9)	37 (23.0)	2.96 (1.65-5.31)		
Smoking type					
Never smokers	92 (57.1)	124 (77.0)	1	<0.001	<0.001
Bidi	27 (16.8)	20 (12.4)	3.17 (1.52-6.61)		
Cigarette	42 (26.1)	17(10.6)	2.75 (1.32-5.73)		
Age at initiation for smoking (years)					
Never	92 (57.1)	124 (77.0)	1		
>30 (Adulthood)	17 (10.6)	20 (12.4)	1.31(0.58-2.96)	<0.001	<0.001
21-30 (Early adulthood)	29 (18.0)	11 (6.8)	4.34 (1.85-10.15)		
1-20 (Upto Adolescence)	23 (14.3)	6 (3.7)	5.92 (2.07-16.91)		
Duration of smoking (years)					
Never	92(57.1)	124 (77.0)	1	0.001	<0.001
1-20	17 (10.6)	12 (7.5)	1.61 (0.64-4.06)		
21-40	27 (16.8)	16 (16.8)	2.50 (1.18-5.32)		
>40	25 (15.5)	9 (5.6)	5.77 (2.28-14.58)		
Consumption of bidi or cigarette (no/day)					
Never	92 (57.1)	124 (77.0)	1	0.001	<0.001
1-9	19 (11.8)	16 (9.9)	1.55 (0.69-3.49)		
10-20	29 (18.0)	13 (8.1)	3.04 (1.35-6.86)		
>20	21 (13.0)	8 (5.0)	5.99 (2.20-16.36)		
Cumulative years of smoking					
Never	92 (57.1)	124 (77.0)	1	<0.001	<0.001
<200	20 (12.4)	19 (11.8)	1.60 (0.77-3.32)		
≥200	49 (30.4)	18 (11.2)	3.89 (2.05-7.34)		

[a]Adjusted for age (continuous); education; income; chewing tobacco and drinking alcohol habits; 1 indicates reference category

Smoking

Nearly 43% of cases and 23% of controls were ever smokers (Table 3). Both forms of smoking emerged as significant risk factors (bidi OR=3.17; 95% CI: 1.52-6.61 in comparison to cigarette OR=2.75; 95% CI: 1.32-5.73). A linear dose-response relationship (for trend, P<0.001 each) can be seen between smoking and risk of UADT cancers in terms of age at initiation (1-20 years, OR=5.92; 95% CI: 2.07-16.91), duration (>40 years, OR=5.77; 95% CI: 2.28-14.58) and daily frequency (>20 times, OR=5.99; 95% CI 2.20-16.36) in their lifetime. The risk of ≥200 cumulative years of smoking tobacco elevated the risk of UADT cancers by approximately four folds (OR=3.89; 95% CI: 2.05-7.34)

Alcohol

Fifty-five percent of the cases were ever alcohol drinkers as compared to about 42% of controls (Table 4). Alcohol drinking did not elevate the risk among ever drinkers as compare to never drinkers (OR=1.06; 95% CI 0.63-1.80). The most common type of alcohol consumed was western-type spirits which elevated the risk by nearly two folds (OR=1.80; 95% CI 1.07-3.00). A linear dose-response relationship emerged between drinking alcohol and incidence of UADT cancers in terms of age at initiation (1-20 years, OR=2.65; 95% CI 1.41-4.99, for trend, P<0.001), duration (>40 years, OR=2.80; 95% CI 1.14-6,85, for trend, P=0.004), frequency (daily, OR=2.21; 95% CI 1.35-3.64, for trend, P=0.011).

Exposure to SHS at home

Approximately 24% cases were exposed to SHS at home in comparison to 10% controls (Table 5). Exposure to SHS during childhood in comparison to adulthood elevated the risk by four times (OR= 4.05; 95% CI 2.06-7.95, for trend, P=0.003).

Combined effects and Population attributable risk of tobacco and alcohol drinking

Table 6 describes the combined effect of chewing and smoking tobacco and drinking alcohol habits with UADT cancer risk. These habits were found to be synergistic with the highest risk (OR= 12.05; 95% CI: 4.61-31.49). Table 7 shows that chewing tobacco as compared to smoking tobacco and drinking alcohol had the highest population attributable risk (79.37% for males and 90.63% for females).

Table 4. Adjusted Odds Ratios and Corresponding 95% Confidence Intervals for UADT Cancers in Males by Drinking Alcohol

Variable name	Cases N (%)	Controls N (%)	Adjusted OR[a] (95% CI)	P-value	P for linear trend
Drinking habit					
Never	72 (44.7)	94 (58.4)	1	0.014	
Ever	89 (55.3)	67 (41.6)	1.06 (0.63-1.80)		
Alcohol type					
Never	72 (44.7)	94 (58.4)	1	0.015	0.004
Toddy	24 (14.9)	26 (16.1)	1.43 (0.75-2.74)		
Western-type spirits	65 (40.4)	41 (25.5)	1.80 (1.07-3.00)		
Age at initiation (years)					
Never	72 (44.7)	94 (58.4)	1	0.004	0.001
>30 (Adulthood)	9 (5.6)	15 (9.3)	0.83 (0.33-2.12)		
21-30 (Early adulthood)	35 (21.7)	31 (19.3)	1.51 (0.82-2.76)		
1-20 (Upto Adolescence)	45 (28.0)	21 (13.0)	2.65 (1.41-4.99)		
Duration of drinking (years)					
Never	72 (44.7)	94 (58.4)	1	0.017	0.004
1-20	30 (18.6)	27 (16.8)	1.39 (0.73-2.66)		
21-40	30 (18.6)	28 (17.4)	1.25 (0.66-2.38)		
>40	29 (18.0)	12 (7.5)	2.80 (1.14-6.85)		
Frequency of drinking					
Never	72 (44.7)	94 (58.4)	1	0.002	0.011
Occasionally	11 (6.8)	19 (11.8)	0.62 (0.27-1.46)		
Daily	78 (48.4)	48 (29.8)	2.21 (1.35-3.64)		
Alcohol intake (unit/day)					
Never	72 (44.7)	94 (58.4)	1	0.04	0.016
<180ml	41 (25.5)	34 (21.1)	0.92 (0.50-1.68)		
≥180ml	48 (29.8)	33 (20.5)	1.16 (0.52-2.58)		

[a]Adjusted for age (continuous); education; income; smoking and chewing tobacco habits; 1 indicates reference category; One drink corresponds to approximately 125 ml of wine; 330 ml of beer; and 30 ml of liquor (i.e., about 12 gm of ethanol)

Table 5. Adjusted Odds Ratios and Corresponding 95% Confidence Intervals for UADT Cancers by Exposure to SHS at Home

Variable name	Cases N (%)	Controls N (%)	Adjusted OR[a] (95%CI)	P-value	P for linear trend
Exposure to second-hand tobacco smoke					
Never	183 (76.3)	215 (89.6)	1	<0.001	
Ever	57 (23.8)	25 (10.4)	2.84 (1.66-4.87)		
Age at initiation of exposure (years)					
Never	183 (76.3)	215 (89.6)	1	<0.001	0.003
Childhood (<16)	42 (17.5)	13 (5.4)	4.05 (2.06-7.95)		
Early to late adulthood (≥16)	16 (6.7)	12 (5.0)	1.73 (0.78-3.82)		

[a]Adjusted for age (continuous), education and income variables; 1 indicates reference category

Discussion

This study provides support for the pathway and lifetime interactions linking exposure of various lifestyle risk factors (chewing and smoking tobacco, drinking alcohol and SHS at home) with incidence of UADT cancers, when assessed with hypothetical models of life-course epidemiology (Gupta and Johnson, 2014). Critical period, critical period with later modifiers, accumulation of risk with independent and uncorrelated insults model, accumulation of risk with correlated insults or risk clustering are the four hypothetical models which can be practically difficult to separate from each other due to significant overlap and simultaneous occurrence (Ben-Shlomo and Kuh, 2002). The critical period model where the early timing of exposure has long lasting effects on anatomical structure or physiological function eventually resulting in cancer was observed. We also confirm the accumulation of risk model in which an increase in number, duration and severity of risk factor exposures across childhood, adolescence and early adulthood causes cumulative damage to

Table 6. Combined Effects of Tobacco and Alcohol Drinking, among Males with Incidence of UADT Cancers

Variable name			Case	Controls	P-value	Adjusted OR[a]	95% CI
Ever chewing	Ever smoking	Ever alcohol taken					
No	No	No	8 (5.0)	43 (26.7)		1.00	
Yes	No	No	51 (31.7)	39 (24.2)	<0.001	7.65	3.12-18.75
No	Yes	No	4 (2.5)	3 (1.9)	0.032	6.89	1.18-40.06
No	No	Yes	1 (0.6)	12 (7.5)	0.551	0.51	0.05-4.72
Yes	Yes	No	14 (8.7)	9 (5.6)	<0.001	8.64	2.63-28.37
Yes	No	Yes	33 (20.5)	27 (16.8)	<0.001	6.39	2.47-16.49
No	Yes	Yes	9 (5.6)	7 (4.3)	0.004	6.85	1.82-25.74
Yes	Yes	Yes	41(25.5)	21 (13.0)	<0.001	12.05	4.61-31.49

[a]Adjusted for age (continuous); education; income; chewing and smoking tobacco and drinking alcohol habits; 1 indicates reference category

Table 7. Adjusted Population Attributable Risk for Tobacco and Alcohol Drinking Habits

Variable name	MalesPopulation Attributable risk %[a] (95% CI)	Females Population Attributable risk %[a] (95% CI)
Chewing tobacco only	79.37 (61.88-96.86)	90.63 (80.01-101.25)
Smoking tobacco only	42.67 (13.62-71.72)	
Drinking Alcohol only	NS	
Chewing and smoking	69.59 (44.67-94.50)	
Chewing and alcohol drinking	75.07 (54.46-95.67)	
Smoking and alcohol drinking	58.53 (30.27-86.79)	
Chewing, smoking and alcohol drinking	86.82 (72.20-101.43)	

[a]Adjusted for age chewing and smoking tobacco and drinking alcohol habits; NS, indicates not significant

the biological system with increasing age, thereby increasing the susceptibility of an individual to cancer (Blane et al., 2007). This idea is complementary to the notion of allostatic load (Gupta et al., 2015). Evidence that risk factors, if correlated, independent or having synergistic effects when two or more habits were present in combination- known as the accumulation model with risk clustering- was also found.

Amongst all the lifestyle habits, our results are consistent with other studies that chewing tobacco is the strongest predictor of UADT cancers in comparison to smoking and drinking alcohol (Sanghvi et al., 1955; Jayant et al., 1977; Sankaranarayanan et al., 1989a; Nandakumar et al., 1990; Wasnik et al., 1998; Dikshit and Kanhere, 2000; Phukan et al., 2001; Balaram. P et al., 2002; Znaor et al., 2003; Basu et al., 2008; Muwonge et al., 2008; Jayalekshmi et al., 2009; Jayalekshmi et al., 2011; Krishna Rao et al., 2016; Gupta et al., 2016). Based on accumulation of risk model, patients who started chewing tobacco during childhood and adolescence (1-20 years) were at more than eleven times higher risk. Similarly, patients who had chewed tobacco for more than 40 years in their lifetime had almost ten times higher risk. These study results are similar to the trends seen for UADT cancers from the past studies (Nandakumar et al., 1990; Rao et al., 1994; Ghosh et al., 1996; Dikshit and Kanhere, 2000; Sapkota et al., 2007; Subapriya et al., 2007; Muwonge et al., 2008; Jayalekshmi et al., 2011). Our study builds on the past evidence that retention of chewing tobacco for a longer duration in the gingivo-labial sulcus (buccal pouch) increases the risk of cancer of buccal mucosa by more than 13 times (Ghosh et al., 1996; Subapriya et al., 2007).

Initiation of smoking during adolescence (1-20 years) and for a duration of more than 40 years increased the risk by much more than five times. Similar results have been reported by many studies in the literature (Rao et al., 1994; Dikshit and Kanhere, 2000; Muwonge et al., 2008; Polesel et al., 2008; Ansary-Moghaddam et al., 2009; Ramadas et al., 2010; Jayalekshmi et al., 2011). However, contradictory results have also been reported (Muwonge et al., 2008; Balaram. P et al., 2002). These differences may be explained by the relatively low prevalence of smoking in these population studies. Bidi emerged stronger than cigarette as a risk factor for UADT cancers. The pooled OR of bidi smoking for UADT cancers was shown to be 3.47 based on 85 studies from the world which is marginally higher than our study (Ansary-Moghaddam et al., 2009). Bidi has been confirmed to be as harmful as cigarettes and may even have a higher toxin yield then cigarettes (Gupta and Mehta, 2000; Rahman and Fukui, 2000). The nicotine content of tobacco in bidis is 21.2mg/g which is higher than that of commercial cigarettes (16.3mg/g) (Malson et al., 2001).

The independent effect of alcohol was observed to be dose dependent over life-course in terms of early age of initiation, daily frequency and duration of drinking for more than 40 years. Our results are in line with a body of literature (Znaor et al., 2003; Subapriya et al., 2007; Muwonge et al., 2008; Tsai et al., 2014). UADT is the first contact site for acetaldehyde, a carcinogen contained in alcoholic beverages which is known to increase the concentration of acetaldehyde in saliva (Balbo et al., 2012). Alcohol drinking also had a synergistic effect on the risk posed for UADT cancers amongst males who chewed

and smoked tobacco. Similar results have been reported as well in other studies on UADT cancers grouped together and various sub-sites in isolation (Sankaranarayanan et al., 1989b; Ferrari et al., 2007; Ansary-Moghaddam et al., 2009; Anantharaman et al., 2011; Ferreira Antunes et al., 2013; Hsu et al., 2014; Prabhu et al., 2014; Tsai et al., 2014).

However, the combined effects and attributable risk due to drinking alcohol in the absence of tobacco did not emerge as a strong predictor for UADT cancers in our study after adjusting for other confounding variables as also reported by others epidemiological studies (Balaram. P et al., 2002; Muwonge et al., 2008; Anantharaman et al., 2011; Schutze et al., 2011). This could be attributed to the likelihood of underreporting of alcohol habit independently without tobacco consumption and the differences in estimating the quantity of alcohol intake per day by our study patients. Furthermore, patients were mainly consumers of western-type spirits and there is an evidence from the literature that drinking arrack in South and Southeast Asia exerts the strongest effect on incidence of UADT cancers (Znaor et al., 2003).

The combined effects of chewing and smoking tobacco as well as drinking alcohol increased the risk for UADT cancers to its maximum as compared to any of these risk factors alone as reflected in Table 6. These results showing the synergistic effect are in line with the past studies (Znaor et al., 2003; Subapriya et al., 2007; Muwonge et al., 2008).

To the best of our knowledge, this is the first ever study in India to explore the relationship between exposure to SHS at home and UADT cancers. Early age at initiation of exposure to SHS (<16 years versus ≥16 years) is associated with an increased risk. This finding confirms the results of some other Western population studies (Lee et al., 2008; Lee et al., 2009; Troy et al., 2013). Children below the age of 16 years tend to spend more time indoors with their family than being outdoors. This subsequently increases their chances of exposure to SHS at home in case their family members/neighbours were active smokers and also increases their chances to initiate smoking as they grow. SHS contains more than 4000 chemicals of which more than 60 are carcinogenic. Specifically, SHS contains high concentrations of nicotine, benzene, poly-cyclic aromatic hydrocarbons, aromatic amines, nitrosamines, benzene, acrylonitrile, arsenic as well as many other carcinogens. These SHS carcinogens are metabolized by passive smokers potentially increasing the cancer risk (Zhu et al., 2003; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004). The importance of public health interventions to reduce this exposure, like promotion of smoke free homes and tobacco cessation at the community level, needs to be underlined in view of its relationship with UADT cancers.

Looking for life-course associations using the accumulation of risk model, there was a positive association between early life initiation of chewing and smoking tobacco, drinking alcohol and exposure to SHS with risk of UADT cancers. Prior research has documented positive association to similar extent between UADT cancer sub-sites (oral cancer) and lifetime exposure to tobacco smoking as well as chewing (Dikshit and Kanhere, 2000; Subapriya et al., 2007; Muwonge et al., 2008; Ramadas et al., 2010; Hsu et al., 2014). However, the lifetime association of alcohol remains controversial (Pelucchi et al., 2008; Hsu et al., 2014)

Limitations

Considering the small number of cases for cancers of larynx, pharynx and oesophagus upper third in comparison to large number of lip and oral cavity cancer cases, we were not able to analyse the effects of risk factors on UADT cancers individually by its sub-sites, hence they were grouped together. Studies conducted in the Western populations have shown that smoking tobacco and alcohol are likely to be potent risk factors for both males and females. We could not explore this relationship amongst females in view of extremely low prevalence of these lifestyle habits in our study population (Anantharaman et al., 2011). A study amongst high-risk Chinese also failed to show that smoking and/or alcohol drinking were associated with risk of UADT cancers among women (Wu et al., 2011). The validity of self-reported exposures also raises concerns: respondents may misclassify their history of tobacco and alcohol because of pressure to quit or social embarrassment: drinking alcohol on a regular basis and in large quantity is still considered a social stigma in Indian society. Furthermore, self-reporting of drinking habits among the occasional consumers may be affected by lower validity due to seasonal variation. Very few cases drank alcohol in the absence of tobacco so we could not compute a meaningful population attributable risk.

Considering the case-control design of our study where the tobacco and alcohol exposure was recorded after the diagnosis of UADT cancer, recall bias remains a substantial threat to the validity of the study. Though selection bias is also a limitation, drawing both the cases and controls from the same population base decreases its likelihood in our study. Under ideal circumstances, cohort study design would be an ideal model for a life-course study. However, due to time and cost constraints, case-control design is an adequate substitute for it.

Our research recognises the theoretical framework of life-course influences of early exposure to various behavioural risk factors as independent and combined predictors of UADT cancers in later stages of life. We considered the accumulation of risk model for assessing the likelihood proposed by each of these risk factors as well as inter-relationships linking their cumulative effects with the incidence of UADT cancers. Research on childhood exposure to SHS and its association with UADT cancers needs further appraisal. Recognition of this life-course perspective can help to improve design public health messages, interventions and policies, with focus on important stages in life for promotion of healthy life-styles, to reduce incidence of UADT and other cancers

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