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CASE CONTROL STUDY: INDIVIDUAL AND COMPARATIVE ASSESSMENT OF RISK FACTORS AS A CAUSE OF ESOPHAGEAL CANCER

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ABSTRACT

Introduction: The association between smokeless tobacco, betel nut and Esophageal Squamous Cell Carcinoma is not much researched area. Hence the assessment of individual risk factors as a cause of esophageal cancer was done in general population.

Method: A case-control study was carried out over a period of 3 years among 690 (230 cases and 460 controls) subjects. All incident squamous cell carcinoma cases were recruited at The Tata Memorial Hospital. A structured pretested questionnaire was used to collect the data through face-to-face interview of the participants.

Results: The ever use of pan, betel nut, tobacco chewing, masheri application, bidi, cigarette smoking and alcohol consumption were having significantly higher odds when the subjects who had never consumed these products were taken as referent. The frequency (amount consumed per day) and duration of use of all the above mentioned entities were also found to be significantly associated with ESCC ($p<0.01$) for all.

Conclusion: All these proven risk factors are potentially preventable at the primary stage, hence health education regarding the hazards need to be incorporated in the school and college syllabus, along with strict implementation of Anti tobacco laws.

Key words: Risk factors, Tobacco chewing, tobacco smoking, betel nut, masheri, esophageal cancer.

INTRODUCTION

In addition to old age related natural death, the diseases which kill the person can be categorized as communicable diseases and non-communicable diseases (NCDs) which includes cardiovascular accidents, COPD, asthma, diabetes and cancer. Globally non-communicable diseases (NCDs) kill 38 million people each year.[1] Therefore, it is essential to monitor the framework on NCDs globally. According to a study every year, roughly 5.8 million Indians die from heart and lung diseases, stroke, cancer and diabetes. [2]

In our work, esophageal cancer was taken as one of the non-communicable diseases for study. In 2012, all over world, there were 14.1 million new cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) of which 400,000 deaths were due to esophageal cancers. While in India there were 1.15 million new cases, 0.6 million cancer deaths and 1.8 million people living with cancer. Of these 7% deaths were due to esophageal cancers.[3]

Various addictions have been described as risk factors for cancer esophagus. Chewing betel nut and betel quid, masheri application, bidi and cigarette smoking are very common addictions in addition to consuming alcohol. Betel quid (pan) is a mixture of areca nut, slaked lime (aqueous calcium hydroxide paste), with or without tobacco, condiments

with or without sweeteners wrapped in a betel leaf. It is chewed and held in the mouth like a quid.[4] *Masheri* also called *mishri*, is made at home by roasting tobacco flakes on a hot griddle until it turns brown or black. It is applied to gums and teeth and retained in the mouth for variable time period.[5] "Indian bidi" contains only a small amount of tobacco dust, rolled in a dried leaf, usually of the Temburni tree (Diospyros melanoxylon) and occasionally of few other varieties depending on the region of the country. *Bidi* tobacco is prepared from sundried *Nicotiana tabacum* leaves which are manually shredded, pounded and sieved to obtain flakes of desired size.[5] All these products are highly addictive containing several carcinogens with high proportional premature mortality.[6]

The present study was undertaken to ascertain and quantify the association of various risk factors which are exclusively prevalent in India for the occurrence of cancer esophagus. Furthermore, poor prognosis of esophageal cancer patients (with only 5–10%, 5-year survival rates) calls for primary prevention as the desired goal. [7]

SUBJECTS AND METHOD

The present study was a hospital based case control study carried out at Tata Memorial Hospital, Parel, Mumbai and Sir J.J. Group of Hospitals, Byculla, Mumbai. The study was carried out over the period of 2 years from April 1996 to May 1998. Sample size was calculated based on relative risk (1.7)[8], prevalence of exposure (p_0= 0.2583)[9], Type I (0.05) and Type II (0.84) error. The required number of cases for the study was 197 and the required number of controls for the study was 197x2= 394 for 1:2 cases: control ratio. To minimize the error further a total of 230 cases and 460 controls (2 controls/ case) was the final sample size. All cancer cases were recruited at The Tata Memorial Centre, which is the national comprehensive centre for the prevention and treatment of all types of cancer. In addition to education and research in Cancer, is recognized as one of the leading cancer centers in India catering patients from all over India and neighboring countries.

Cases selection was based on histopathologically confirmed diagnosis of Esophageal Squamous Cell Carcinoma irrespective of their degree and cases not having any previous cancer history. Patients with adenocarcinoma or any other tumors of the oesophagus were excluded.

Controls were inpatients free from cancer of any organ, admitted for a wide spectrum of acute conditions belonging to the age of 30 years and above, hospitalized at Sir J.J. Group of Hospitals during the study period. Cases and controls were broadly matched for age (+/- 2years). Due clearance was obtained from Institutional Ethical Committee and Hospital administration. The study participants were informed about the purpose and method of study. Written consent was obtained from participating patients. The cases and controls were personally interviewed by investigator. Measurement of exposure was done by taking detailed history of cases and controls on the predesigned and pretested questionnaire. Information on age, sex, education level, socio-economic status, family history of esophageal cancer (first degree relatives), clinicpathological symptoms and dietary habits was collected. Details of personal habits that included chewing betel quid and betel nut, tobacco, masheri application, bidi and cigarette smoking and consumption of alcohol was taken. Those who smoked at that time were referred to as current smokers, while ex-smokers were those who had stopped smoking 2 or more years before the date of diagnosis or interview.

Statistics

Odds ratio calculations with 95% confidence interval and then Chi square Trend was calculated for different groups. P<0.05 was considered statistically significant. Multiple Logistic Regression Analysis was employed to examine the interactions and joint effect of independent risk factors, using the computer program MLVTR (Release05/89, Educado Franco, N. Campus Filho). Attributable Risk Proportion (ARP) and Population Attributable Risk Proportions (PARP) with the 95% confidence limits was calculated for those risk factors which were significant in the final model in the multiple logistic regression analysis.[10]

RESULT

In this study there are 230 cases and 460 controls. The largest proportion of cases are in the 51-60 age group, followed by >60 years. The ratio of men to women was 1.99:1 for cases and 2.43:1 in controls. No significant association was detected with socioeconomic status.

In Tables 2 (a, b, c): The ever use of pan chewing [OR= 1.58, 95% CI =1.14-2.19 ;p=0.01], betel nut chewing [OR= 2.67 (1.91-3.73);p0.001], tobacco chewing [OR= 1.50, 1.06-2.12);p=0.019], masheri application [OR=1.84 (1.20-2.82); p=0.004], bidi smoking [OR= 3.19 (2.24-5.53);p=0.0001], cigarette smoking [OR = 2.70 (1.78-4.09);p=0.0001] and alcohol consumption [OR= 2.95 (2.06-4.22);p= 0.0001] were having significantly higher odds when the subjects who had never consumed these products were taken as referent.

Table 1: Distribution of age, sex and socio-economic status among cases and controls

Variables	Cases (N=230) (%)	Controls (N=460) (%)
Age Group		
≤ 30	3 (1.3)	15 (3.26)
31-40	26 (11.3)	78 (16.96)
41-50	59 (25.65)	130 (28.26)
51-60	75 (32.61)	145 (31.52)
≥ 60	67 (29.13)	92 (20)
Sex		
Male	153 (66.52)	326 (70.87)
Female	77 (33.48)	134 (29.13)
Socioeconomic status		
Upper	15 (6.52)	52 (11.3)
Upper Middle	40 (17.39)	73 (15.87)
Middle	52 (22.61)	125 (27.17)
Upper Lower	58 (25.22)	108 (23.48)
Lower	65 (28.26)	104 (22.61)

Table 2(a): Risk Factors (Pan chewing and Betel nut) along with the frequency and duration

Risk Factors	Cases (n=230) (%)	Controls (n=460) (%)	OR (CI)	P value
Family History				
No	216 (93.92)	447 (97.18)	Referent	0.037
Yes	14 (6.09)	13 (2.83)	2.23 (1.03-4.83)	
Pan chewing				
No	155 (67.4)	352 (76.53)	Referent	0.01
Yes	75 (32.61)	108 (23.48)	1.58 (1.14-2.19)	
Intensity				
Never use	127 (55.22)	324 (70.44)	Referent	<0.001*
<5 times/day	45 (19.57)	92 (20)	1.25(0.83-1.89)	
5-9 times/day	12 (5.22)	12 (2.61)	2.55(1.12-5.82)	
≥10times/day	18 (7.83)	4 (0.87)	11.48(3.8-34.6)	
Ex-chewer	28 (12.18)	28 (6.09)	2.55(1.46-4.48)	
Duration (in years)				
Never	127 (55.22)	324 (70.44)	Referent	<0.01*
≤ 10	22 (9.57)	39 (8.48)	1.43 (0.8-2.51)	
11—20	16 (6.96)	38 (8.27)	1.07(0.58-1.99)	
≥ 21	37 (16.09)	31 (6.74)	3.04(1.81-5.11)	
Ex-Chewers	28 (12.18)	28 (6.09)	2.55(1.46-4.48)	
Betel Nut Chewing				
No	121 (52.61)	344 (74.79)	Referent	0.001
Yes	109 (47.4)	116 (25.22)	2.67(1.91-3.73)	
Intensity				
Never	121 (52.61)	344 (74.79)	Referent	<0.0001*
1/2 nut/day	26 (11.31)	62 (13.48)	2.31(1.32-4.03)	
1 nut/day	43 (18.7)	62 (13.48)	1.97(1.27-3.06)	
≥ 2 nut/day	40 (17.4)	22 (4.79)	5.20(2.97-9.10)	
Duration (in years)				
Never	121 (52.61)	344 (74.79)	Referent	<0.001*
≤ 10	35 (15.22)	49 (10.66)	2.03(1.26-3.48)	
11—20	26 (11.31)	41 (8.92)	1.8 (1.06-3.07)	
21-31	21 (9.14)	15 (3.27)	4.0 (2.0-8.01)	
≥ 31	27 (11.74)	11 (2.4)	7.0 (3.37-14.54)	

*p value for trend

The frequency (amount consumed per day) and duration of use of all the above mentioned entities were also found to be significantly associated with ESCC (p<0.01) for all.

On unconditional multiple logistic regression analysis, ESCC was significantly associated with Bidi (OR= 2.604,95%CI.1.701-3.984, p< 0.001), Cigarette smoking (OR=2.584,95% CI. 1.6-4.167, p=0.0001), Mashiri (OR= 1.894,95% CI.1.156-3.106, p=0.0113), Alcohol (OR= 2.320, 95% CI. 1.504-3.584, p= 0.0001) and lastly Betel nut (OR= 2.646, 95% CI. 1.805-3.876, p=0.0000). No significant association was detected with family history.

Table 2(b): Risk Factors (Tobacco chewing, Mashiri application, Bidi and Cigarette smoking) along with the frequency and duration

Risk Factors	Cases (n=230)	Controls (n=460)	OR (CI)	p value
Tobacco chewing				
No	152 (66.09)	343 (74.57)		0.019
Yes	78 (33.92)	117 (25.44)	1.5(1.06-2.12)	
Intensity per day				
Never	138 (60)	322 (70)	Referent	<0.005*
< 5	35 (15.22)	63 (13.7)	1.25(0.79-1.98)	
5-9	23 (10)	39 (8.48)	1.33(0.77-2.31)	
≥10	20 (8.7)	15 (3.27)	3.01(1.50-6.05)	
Ex-chewer	14 (6.09)	21 (4.57)	1.56(0.77-3.16)	
Duration (in years)				
Never	138 (60)	322 (70)	Referent	<0.01*
≤ 10	21 (9.14)	45 (9.79)	1.09(0.63-7.90)	
11—20	12 (5.22)	35 (7.61)	0.80(0.40-1.59)	
21-30	22 (9.57)	28 (6.09)	1.83(1.01-3.31)	
≥31	23 (10)	9 (1.96)		
Ex-chewer	14 (6.09)	21 (4.57)	1.56(0.77-3.16)	
Mashiri Application				
No	184 (80)	405 (88.05)		0.004
Yes	46 (20)	55 (11.96)	1.84(1.20 -2.82)	
Intensity per day				
Never	184 (80)	405 (88.05)	Referent	<0.01
Once	26 (11.31)	36 (7.83)	1.6(0.94-2.73)	
>Twice	20 (8.7)	19 (4.14)	2.33(1.31-4.14)	
Duration (in years)				
Never	184 (80)	405 (88.05)	Referent	<0.01*
≤ 20	17 (7.4)	29 (6.31)	1.31(0.70-2.44)	
21-40	10 (4.35)	9 (1.96)	2.47(0.99-6.18)	
≥41	19 (8.27)	17 (3.7)	2.49(1.26-6.87)	
Bidi Smoking				
No	136 (59.14)	378 (82.18)		0.0001
Yes	94 (40.87)	82 (17.83)	3.19 (2.24-5.53)	
Intensity per day				
Never	119 (51.74)	349 (75.87)	Referent	<0.001*
≤ 10	37 (16.09)	42 (9.14)	2.59(1.59-4.22)	
11-20	29 (12.61)	28 (6.09)	3.06(1.75-5.35)	
≥ 21	28 (12.18)	12 (2.61)	6.85(3.38-13.90)	
Ex-chewer	17 (7.4)	29 (6.31)	1.74(0.92-3.28)	
Duration (in years)				
Never	119 (51.74)	349 (75.87)	Referent	<0.001*
≤ 10	19 (8.27)	31 (6.74)	1.79(0.97-3.29)	
11—20	27 (11.74)	25 (5.44)	3.18(1.78-5.69)	
21 –30	23 (10)	16 (3.48)	4.24(2.17-8.29)	
≥ 31	25 (10.87)	10 (2.18)	7.35(4.02-13.43)	
Ex-smoker	17 (7.4)	29 (6.31)	1.74(0.9-3.28)	
Cigarette Smoking				
No	172 (74.79)	409 (88.92)		0.0001
Yes	58 (25.22)	51 (11.09)	2.70(1.78-4.09)	
Intensity per day				
Never	152 (66.09)	378 (82.18)	Referent	<0.001*
< 10	36 (15.66)	42 (9.14)	2.15(1.33-3.49)	
11 -20	15 (6.53)	7 (1.53)	5.35(2.14-13.42)	
≥ 21	7 (3.05)	2 (0.44)	8.75(1.80-42.60)	
Ex-smoker	20 (8.7)	31 (6.74)	1.63(0.90-2.95)	
Duration (in years)				
Never	152 (66.09)	378 (82.18)	Referent	<0.001*
≤ 10	14 (6.09)	21 (4.57)	1.68(0.83-3.39)	
11—20	12 (5.22)	15 (3.27)	2.0(0.91-4.37)	
21 –30	18 (7.83)	11 (2.4)	4.1(1.89-8.89)	
≥ 31	14 (6.09)	4 (0.87)	8.5(2.75-26.24)	
Ex-smoker	20 (8.7)	31 (6.74)	1.63(0.92-2.95)	

*p value for trend

Table 2(c): Risk Factors (Alcohol) along with the frequency and duration

Risk Factors	Cases (n=230)(%)	Controls (n=460)(%)	OR (CI)	p value
Alcohol				
No	141 (61.31)	379 (82.4)		0.0001
Yes	89 (38.7)	81 (17.61)	2.95 (2.06-4.22)	
Amount (ml/day)				
Never	114 (49.57)	333 (72.4)	Referent	<0.001*
≤ 180	29 (12.61)	32 (6.96)	2.68(1.55-4.62)	
180 – 375	22 (9.57)	21 (4.57)	3.09(1.64-5.83)	
375 – 750	31 (13.48)	25 (5.44)	3.65 (2.07-6.44)	
≥ 750	7 (3.05)	3 (0.66)	6.85 (1.74-26.9)	
Ex-Drinker	27 (11.74)	46 (10)	1.74 (1.03-2.93)	
Duration (in years)				
Never	114 (49.57)	333 (72.4)	Referent	<0.001*
≤ 10	24 (10.44)	32 (6.96)	2.21 (1.25-3.91)	
11 – 20	33 (14.35)	37 (8.05)	2.62 (1.50-4.39)	
21 –30	15 (6.53)	9 (1.96)	4.91 (2.09-11.53)	
≥ 31	17 (7.4)	3 (0.66)	16.68 (4.80-57.96)	
Ex-Drinker	27 (11.74)	46 (10)	1.74 (1.03-2.93)	

*p value for trend

Table 3: Multiple Logistic Regression Analysis of Cancer of Esophagus

Term	P-Value	Or	Lower	Upper
Hereditary	>0.05	1.898	0.743	4.854
Bidi Smoking	<0.001	2.604*	1.701	3.984
Cigarette Smoking	0.0001	2.584*	1.600	4.167
Masheri	0.0113	1.894*	1.156	3.106
Alcohol	0.0001	2.320*	1.504	3 .584
Betel Nut	<0.001	2.646*	1.805	3.876

* Significant. # Data has been classified into dichotomous type (Yes/No) for multiple logistic regression analysis

Table 4: Attributable Risk Proportions (ARP) & Population Attributable Risk Proportion (PARP) Of Significant Risk Factors.

Risk Factors	ARP	95% C.I.	PARP	95% C.I.
Bidi Smoking	0.62	0.41 – 0.75	0.23	0.14 –0.30
Cigarette Smoking	0.61	0.37 –0.76	0.15	0.06 –0.26
Masheri	0.47	0.13 –0.68	0.09	0.01 –0.20
Alcohol	0.57	0.33 –0.72	0.19	0.09 –0.33
Betel Nut	0.62	0.45 –0.74	0.29	0.17 –0.42

The highest ARP was for betel nut (ARP=0.62) and masheri (ARP=0.47) was having the lowest ARP, hence, attributing these exposures towards the development of cancer of oesophagus, thus confirming their etiological role.

DISCUSSION

We found the largest proportion of ESCC cases were in the 51-60 age group (32.6%), followed by >60 years (29.13%), ESCC was more prevalent in patients with low socioeconomic status (28.26%) and males (66.52%); approximately two times higher than females; family history had no significant impact on occurrence of ESCC on unconditional multiple logistic regression analysis. All these findings were similar to previous studies.[11,12,13,14,15]

Our study showed that the ever use, frequency and duration of pan chewing (with or without tobacco), betel nut chewing (with or without tobacco), bidi smoking, cigarette smoking and alcohol consumption were associated with significantly higher risk of ESCC. Similar findings have been reported from various Asian and European studies.[7, 15, 16, 17]

Congestion and erosion of the esophageal mucosa had been observed among the betel (areca) nut chewers, suggesting direct mucosal contact with swallowed areca nut juice might have contributed to the ESCC. *In vitro* studies have shown that areca nut`s alkaloid – arecoline is a precursor for at least four N-nitrosamines and two of which are carcinogens.[19] Further contamination of areca nuts has also been found by fungi such as Aspergillus flavus, A. niger and Rhisopus sp. which can produce carcinogenic aflatoxins.[18]

In present study betel nut use had the highest Odds (OR= 2.646, 95% CI. 1.805-3.876, p<0.0001, as Phukan et al too reported betel nut as one of the most important risk factor for oesophageal cancer in Assam. [8]

Sankaranarayanan-R reported the risk is increasing with the rise in duration (> 21 years OR- 1.15, 95% CI-0.63-2.10). In our study also, only after a duration of more than 21 years of pan chewing, was significantly higher when the subjects who never used it were taken as reference, the Odds ratio (OR=3.04; 95% CI=1.81-5.11). This may be because of the fact that pan quid is spit out and not swallowed and a long latent period may be necessary for the development of cancer of the esophagus. [9]

We found significant correlation between masheri application and occurrence of esophageal cancer (OR= 1.894, 95% CI.1.156-3.106, p=0.0113). In the Indian context, relevant and supporting human studies could not be found. In aqueous extracts of black and brown *masheri,* levels of preformed N-Nitrosonornicotine (NNN) and N-nitrosoanatabine (NAT), benzapyrene and nicotine were higher than in tobacco used for their preparation. It is also reported that HCN and phenols have tumor promoting and co-carcinogenic activities, detected in both brown and black *masheri*. [5]

As regards to smoking, adding filters in cigarettes might reduce the amount of carcinogens inhalation. An analysis of tobacco specific nitrosamines (TSNA) in cigarette and bidi, tobacco fillers of a filtered cigarette showed minimum amounts of NNN, NAT and NNK but the levels were higher in non-filtered bidi and cigarette fillers.[19] In case of alcohol, the metabolic products of ethanol are acetaldehyde and free radicals. The free radicals are responsible for alcohol associated carcinogenesis through their binding to DNA and proteins, which

destroy foliate leading to secondary hyper proliferation.[20] Additionally, alcohol can act as a solvent, helping other harmful chemicals, such as those in tobacco smoke, enter the cells lining the upper digestive tract more easily. This explains why the combination of smoking and drinking is much more likely to cause cancer.

Limitations of study:

Due to hospital based study Berksonian bias is inherent and thus limits the generalizability of the study. The Recall Bias was minimized by taking detailed history of the patients about the exposure of various risk factors. Also because of the hospitalized control group, overall recall bias might have been comparable in both the groups. There were many potential confounds like cigarette smoking, bidi smoking, alcohol consumption etc. In this study, the effect of potential confounders was partly controlled by frequency matching for age. But as the potential numbers of confounders was large, mathematical modeling was resorted to in the analysis stage. This was done in the form of employing Multiple Logistic Regression Analysis.

CONCLUSION

The risk factors like betel nut, betel quid, masheri, bidi and cigarette smoking and alcohol are all found to be associated with esophageal squamous cell carcinoma. All these risk factors are excessively prevalent in a country like India. A significant reduction in the risk among ex- cigarette and bidi smokers and ex- alcohol drinkers was also observed. The frequency (amount consumed per day) and duration of use of all the above mentioned entities were also found to be significantly associated with ESCC. Inspite of knowing or creating awareness about the risk factors over the period of time, the disease prevalence is still increasing.

RECOMMENDATION

All these proven risk factors are potentially preventable at the primary stage, hence health education regarding the hazards need to be incorporated in the school and college syllabus (curriculum). For the masses, strict implementation of Anti- tobacco laws at public places, workplaces and in the community is necessary and should be embarked upon so as to limit the use of noxious substances. Influencing the socio-cultural customs and beliefs regarding tobacco in the community is important for preventing the initiation of tobacco use. As most women consumed masheri, which is available at a very low cost, it emphasizes the need of having system in place to impose taxes on all tobacco products including non- manufactured tobacco.

Reduced risk was observed amongst ex- smokers and drinkers, thus an effective secondary prevention strategy to encourage cessation of the above risk behavior can be pursued.

Most importantly, the success of tobacco cessation is determined by combination of the initiatives taken by the tobacco users to quit and the support system offered by family, community and the healthcare professionals.

REFERENCES

1. Non-communicable diseases. Available at: http://www.who.int/mediacentre/factsheets/fs355/en/ Accessed on May 12th, 2015
2. India: first to adapt the Global Monitoring Framework on non-communicable diseases (NCDs) Available at: http://www.who.int/features/2015/ncd-india/en/ Accessed on May 12th, 2015
3. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed on May 15th, 2015.
4. Jussawalla-DJ; Deshpande-VA: Evaluation of cancer risk in tobacco chewers and smokers: An epidemiology assessment: Cancer; 1971; 28(1): 244-252.
5. Bhisey R A. Chemistry and toxicology of smokeless tobacco. Indian J Cancer 2012; 49:364-72.
6. Phukan, R.K., Ali, M.S., Chetia, C.K., and Mahanta, J. Betel nut and tobacco chewing; potential risk factors of cancer of oesophagus in Assam, India. Br J Cancer. 2001; 85: 661–667
7. Akhtar S(1), Sheikh AA, Qureshi HU: Chewing areca nut, betel quid, oral snuff, cigarette smoking and the risk of oesophageal squamous-cell carcinoma in South Asians: a multicentre case-control study :Eur J Cancer ; 2012 Mar; 48(5):655-61.
8. Rao DN; Sanghvi LD; Desai PB: Epidemiology of Oesophageal cancer: Seminar- Surg-Oncol: 1989: 5 (5); 351-4.
9. Sankaranarayanan-R; Duffy-SW; Padmakumary-G; Nair-SM; Day-NE; Padamanbhan-TK: Risk factors for Cancer of the Oesophagus in Kerala, India; International Journal of Cancer; 1991; 49 (4): 485-9
10. Holland Walter. W; Roger Detels; Knox George: Oxford Textbook Of Public Health: 2nd Edition: United Kingdom: Oxford University Press; 1991: pg 121-144
11. Hashibe M(1), Boffetta P, Janout V, Zaridze D, Shangina O, Mates D, Szeszenia-Dabrowska N, Bencko V, Brennan P: Esophageal cancer in Central and Eastern Europe: tobacco and alcohol : Int J Cancer; 2007 Apr 1:120(7):1518-22.
12. Dar NA(1), Bhat GA, Shah IA, Iqbal B, Makhdoomi MA, Nisar I, Rafiq R, Iqbal ST,Bhat AB, Nabi S, Shah SA, Shafi R, Masood A, Lone MM, Zargar SA, Najar MS, Islami F, Boffetta P: Hookah smoking, nass chewing, and oesophageal squamous cell carcinoma in Kashmir,India : Br J Cancer: 2012 Oct 23;107(9):1618-23.
13. Wynder-Ernest L; Bras-Iwin J: A study of etiological factors in cancer of the oesophagus: Cancer; 1961; 14(2): 389-443.
14. Vizcaino-AP; Parkin DM; Shinner ME: Risk factors associ-

ated with oesophageal cancer in Buawayo; Zimbabwe: British Journal of Cancer: 1995; 72(3) p 769-73.

15. Akhtar S: Areca nut chewing and esophageal squamous-cell carcinoma risk in Asians: a meta-analysis of case-control studies: Cancer Causes Control; 2013 Feb ; 24(2):257-65

16. Ramesh-C: Oesophageal Cancer: an epidemiological study in India : Diss: Abstr-Int-C; 1994; 55(3):867

17. Hoffmann, D., Brunnemann, K.D., Prokopczyk, B., and Djordjevic, M.V. Tobacco-specific N-nitrosamines and areca-derived N-nitrosamines: chemistry, biochemistry, carcinogenicity and relevance to humans. J Toxicol Environ Health. 1994; 41: 1–52

18. Borle RM and Gupta DS: Fungal contamination of Arecanut. *Indian J PatholMicrobiol: 1987;* **30**: 357–360

19. Nair J, Pakhale SS, Bhide SV. Carcinogenic tobacco specific nitrosamines in Indian tobacco products. Food and Chemical Toxicology: 1989; 27:751.3.

20. Anand P, Ajaikumar BK, Sundaram C, Kuzhuvelil BH, Sheeja TT, Oiki SL, SungB, Bharat BA: Cancer is a Preventable Disease that Requires Major Lifestyle Changes. Pharm Res: 2008; 25, 2097-2116.