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RESEARCH ARTICLE

TOBACCO EXPOSURE AND ALCOHOLIC USAGE AS RISK FACTORS OF HEAD AND NECK CANCER

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ABSTRACT

Background: Among all other cancers, Head and Neck cancer (HNC) are more predominant throughout the world and sixth most common malignancy with highest morbidity and mortality. Recent reports says that 57.5% of global head and neck cancers occur in Asia. In India it accounts for 30% of all cancer incidences. Hence our objective is to determine the etiology of head and neck cancer, incidence and factors which contribute to the occurence and distribution of head and neck cancer in North Coastal Andhra Pradesh.

Materials and Methods: 123 confirmed diagnosed patients of head and neck cancer from King George Hospital, Visakhapatnam were enrolled in this prospective study. Data collected about demographic factors, area of residency, personal habits like tobacco and alcohol usage with anatomy of disease, stage and grade of the disease. The collected data was analysed by using ANOVA and Medcalc® software.

Results: 76 male and 47 female head and neck cancer patients were studied in the present study with mean age of 54.18 years. Higher number of patients were found in 41-70 years of age group with tobacco usage. Any form of tobacco usage with or without alcoholic exposure showed prominent significance in both genders ($p=<0.05$). Anatomy of the disease, stage and grade of the disease not differentiated by any of the variables like habit, occupation, gender and age.

Conclusion: Head and neck cancer with risks increasing in a dose dependent fashion and declining with the duration of smoking cessation proven in this study ($p<0.001$). Tobacco exposure and alcoholic usage increases the risk of head and neck cancer in both males and females.

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INTRODUCTION

Cancer is a complex group of diseases with many possible causes. The known causes of cancers includes lifestyle factors such as tobacco use, diet, and less physical activity; certain types of infections; environmental exposure to different types of chemicals and radiation and genetic factors. Genetic predisposition alone may not be responsible for causing cancer but a combination of susceptibility genes and exposure including environmental factors could contribute to the development of non-familial, sporadic cancers and also has been established that environmental factors play a major role in most of the sporadic cancers. Among all other cancers, head and neck cancer (HNC) are more predominant throughout the world and sixth most common malignancy with highest morbidity and mortality.

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Usually head and neck cancers include the sites of lip, tongue, gum, floor of mouth, palate, mucossa, oropharynx, nasopharynx, hypopharynx, and larynx. Recent reports says that 57.5% of global head and neck cancers occur in Asia. In India it accounts for 30% of all cancer incidences. Many epidemiological studies proved that heavy smoking and alcohol intake are also important risk factors in many cancers including head and neck cancers. Occupational exposure to carcinogens, infections and dietary habits, are additional risk factors that have been associated with increased cancer risk (Vijay Kuma and Suresan, 2012). In recent years, evidence has accumulated to support the hypothesis that diet may also play an important etiological role in development of the disease, and 10-15% of (SCCHN) cases in Europe are associated with a low intake of fruit and vegetables (Nicolotti *et al*., 2011; Chuang *et al*., 2012; Stott-Miller *et al*., 2012).

Oral cancer most commonly occurs in middle-aged and kmalignancies is also being documented in younger adults in

recent years (Llewellyn *et al*., 2004; Rodriguez *et al*., 2004). With an estimated 2.5 million cancer and nearly 0.8 million new cases adding up by the year scientific projection show there could be a 50% increase in cancer death by the year 2015 (Anmol Mathur *et al*., 2007). Oral cancers accounts for more than five hundred thousand newly diagnosed cases every year worldwide (Massimo *et al*., 1995). Generally, the highest incidence rates of oral cancer are found in South-East Asia, and Central and Eastern Eurpoe for both males and females (Jemal *et al*., 2011).

In India, the use of 'pan' (a combination of betel nut, areca nut, lime and tobacco) as well as reverse smoking (smoking a cheroot with the burning end inside the mouth) are responsible for the high incidence of oropharyngeal cancer. The use of betel quid also has become culturally accepted practice in India, which has now become a susceptible health problem. However, all individuals exposed to the same kind and dose of carcinogen do not develop cancer. Hence it is now clear that cancer development is not only due to exogenous or endogenous carcinogens but their interactions with genes that are responsible in the detoxification of these carcinogens, repair of DNA damage and control of cell signalling and cell cycle. Genetic variations in a number of critical regulatory pathways modify the tobacco related cancer risk (Wu *et al*., 2004). A recent report by Charoenchai Puttipanyalears (2014) showed Alu hypomethylation is likely to be associated with multistep oral carcinogenesis in oral cancers and also caused by Human Papillomaviruses (Charoenchai Puttipanyalears *et al*., 2014; Pradit Rushatamukayanunt *et al*., 2014). While on one hand genetic aberrations constitute irreversible changes or mutations in the DNA coding sequences resulting in over expression/increased activity or in action, of key oncogenes and tumor suppressor genes, respectively (Lingen *et al*., 2011; Saintigny *et al*., 2011)**.** This screening in cancer patients continues to fulfilling the aim of unraveling and understanding subsequent disease mechanism and targets population for interventions.

MATERIALS AND METHODS

The present study includes 123 histopathologically confirmed cases of head and neck cancer, staging assessed and classified as per TNM guidelines. Patients from various districts of coastal Andhra Pradesh admitting in Department of Radiotherapy, King George Hospital, Visakhapatnam from 2011 to 2012 were enrolled in this study. The patients were consented to participate and assured the confidentiality of all information about them. Details about their education, occupation, family history of cancer, present and past medical history, diet pattern, smoking habit, history of alcohol intake, exposure to any environmental pesticides/carcinogens were recorded in a structured questionnaire at the time of interview. The data were analysed statistically by using ANOVA and Medcalc software.

Statistical analysis

Statistical analysis was done on the data collected for comparing age, sex ratio, anatomy of disease and habitual factors by using odds ratio(ANOVA).The significance of correlation for the present data was calculated by Medcalc software (P value <0.05 is considered as statistically significant).

RESULTS

Table 1 showing, 123 patients confirmed with malignancies were taken in this study constituting 76 (61.78%) males and 38 (38.21%) females. Mean age for all HNC patients was 54.18 years (range 21-80 years). Mean age for males was 55.40 years and for females 52.95 years. Little variation was found in between male and female age groups. Higher number of patients found to be in 41-70 years age group in both males and females. It is observed that the frequencies of HNC males and females in rural area were 68.42% and 65.95% respectively whereas the frequency of HNC males was 31.57% and females was 34.04% in urban area. Out of 123 HNC patients,67.4% cancer patients belongs to rural area and 32.5% cancer patients belongs to urban area. From the table it is clear, that majority of the cancer patients settled in rural areas are more affected than urban areas.

In this study we could not find any association with age group, rural and urban residency where p value showed >0.05. The occupation of the patients recorded in Table 1, shows 40.65% of the cancer patients (males and females) are labour (daily wager working at various industries), 24.39 % were households not working anywhere, 19.51% are agricultural workers where most of them exposed to pesticides and other environmental carcinogens. 15.44% cancer patients are private employees. While considering the occupation more cancer patients were found to be daily wagers. Odds ratio shows significant results for both males and females in relation to occupation where all p values showed <0.05. The frequencies of lower socio economic status of males and females of cancer patients were 34.21% and 27.63% respectively whereas the frequency of middle socio economic status of males was 65.78% and females was 55.31%.While considering all HNC patients, 38.21% cancer patients belongs to lower income group and 61.78% cancer patients belongs to middle income group. There is no statistical significance between socio-economic status and cancer patients.

Regarding to anatomy of the disease, the frequency of pharynx (60.16%) was more common than frequency of oral cavity (26.01%) and larynx (13.82%). With respect to gender, males were more prone to cancer. In males and females, Pharynx (63.15% and 55.31%) was the most affected site than oral cavity (21.05% and 21.05%) and larynx (15.78% and 10.68%). Hence pharyngeal cancer predominates the oral and laryngeal cancers. Odds ratio for anatomy of disease and gender were found to be non significance where p value is >0.05. Table 2 demonstrates the frequency of personal habits like smoking and alcohol consuming were presented. Personal habits like smoking were found to be high in both males and females of this study. In males 27 (35.53%) bidi/cigarette smokers, 5 (6.58%) reverse smokers, 37 (48.68%) tobacco chewers and 7 (9.21%) non smokers were found. In females 6 (12.76%) smokers, 14 (25%) reverse smokers, 8 (29.79%) tobacco chewers and 19 (40.42%) non smokers were observed.

Table 1. Demographic characteristics of the study subjects

Variables	Male (N=76)	Female (N=47)	Odds Ratio	95% CI	pValue
Age Group					
21-30	1(1.31%)	3 (6.382%)	0.1	0.02- 1.9	0.16
31-40	9 (11.84%)	5 (10.638%)	1.1	0.35 – 3.6	0.83
41-50	18 (23.68%)	08(17.021%)	1.5	0.6 – 3.82	0.38
51-60	24(31.58%)	19 (40.42%)	0.7	0.3 – 1.4	0.31
61-70	15 (19.7%)	10 (21.27%)	0.9	0.4 – 2.2	0.83
71-80	08 (11.8%)	02 (4.25%)	2.9	0.6 – 14.4	0.17
Area of Living					
Rural	52(68.42%)	31(65.95%)	1.1	0.5 – 2.4	0.78
Urban	24(31.57%)	16(34.04%)	0.9	0.4 – 1.9	0.77
Occupation					
Private Employee	19 (25%)	0	32.2	1.89 – 5.47	<0.05
Farmer	20 (26.3%)	4 (8.51%)	3.83	1.2 – 12.0	<0.05
House Holds	0	30(63.8%)	0.00	0.00 -0.06	<0.05
Daily Wager	37 (48.7%)	13 (27.7%)	2.5	1.1 -5.4	<0.05
Socio-Economic Status					
Lower Income	26(34.21%)	21(27.63%)	0.6	0.30 – 1.35	0.25
Middle Income	50(65.78%)	26(55.31%)			
Site of Disease					
Larynx	12 (15.78%)	05 (10.68%)	1.6	0.52-4.8	0.4
Oral Cavity	16 (21.05%)	16 (21.05%)	0.52	0.2-1.2	0.1
Pharynx	48 (63.15%)	26 (55.31%)	1.4	0.7-2.9	0.4

Table 2. Habitual factors and association with Head and Neck cancer risk

Variables	Male (N=76)	Female (N=47)	Odds Ratio	95% CI	pValue
Tobacco Exposure Type					
Bidi/Cigarette Smokers	27 (35.5%)	6(12.7%)	3.8	1.47 - 10.0	<0.05
Reverse Smokers	5 (6.6%)	14 (25%)	0.17	0.05– 0.5	<0.05
Tobacco Chewers	37 (48.7%)	8(29.8%)	4.6	1.9–11.2	<0.05
Non smokers or Non tobacco Chewers	7 (9.21%)	19 (40.4%)	0.14	0.05– 0.4	<0.05
Drinking Habit					
Drinkers	46 (60.52%)	08 (17.02%)	7.47	3.1-18.2	<0.05
Non drinkers	30 (39.5%)	39 (82.9%)			

The frequencies of cancer patients (both males and females) of bidi/cigarette smokers ,reverse smokers, tobacco chewers and non smokers are 26.82%,15.44%,36.58% and 21.13% respectively. Tobacco chewing predominates other habits in HNC patients. Gender with smoking habits (Table 2) are statistically significant (p values showed < 0.05). Frequency of alcohol consuming males was 60.52%, females was 17.02% and total frequency was 43.09%,whereas the frequencies of non drinker males, females and total were 39.47%,82.97% and 56.09% respectively. In HNC patients alcoholic males were more than females. Correlation was done for gender with drinking habit and found to be significant where p value is <0.05.

The frequencies of HNC patients in relation with the tobacco exposure period were presented in Table 3.The frequency of tobacco exposure period increases with increase of age. The frequency of non tobacco exposure was 22.76%. Majority of the cancer patients exposed to tobacco are above 40years. Irrespective of duration of exposure with tobacco all the cancer patients shows significant results (P=<0.05). The mean values of drinking habit, smoking habit, both drinking and smoking habit were exhibited in Table 4.The two way ANOVA test between two variables, i.e., gender with drinking habit, smoking habit, smoking and drinking habits, non smokers and non drinkers of the HNC patients were done.

Table 3. Tobacco exposure duration of the cancer patients in relation to prevalence of head and neck cancer

Factor	N	Frequency	Mean	P value
Non tobacco exposure	28	22.76%	3.9286	
Less than10 year exposure	2	2.10%	3.0000	
11- 20 years exposure	6	6.31%	2.1667	
21 -30 years exposure	20	21.05%	2.1500	< 0.05
31- 40 years exposure	28	29.47%	2.0357	
41 and above years exposure	39	41.05%	2.0769	

Table 4. Smoking and Drinking habits of the cancer patients in relation to prevalence of head and neck cancer

Habit	Mean	Std.Error	95% CI	pValue
Drinking habit				
Drinkers (n=54)	1.14	0.08	0.97 – 1.3	
Non drinkers (n=69)	1.6	0.05	1.47 – 1.6	<0.05
Smoking Habit				
Bidi/Cigaretts (n=33)	1.22	0.07	1.08 – 1.3	
Reverse Smoking (n=19)	1.63	0.09	1.44 – 1.8	
Tobacco - Chewing (n=45)	1.2	0.06	1.06 – 1.3	<0.05
Non-Smoker (n=26)	1.4	0.1	1.1 – 1.7	
Drinking with Smoking Habit				
Drinking with Bidi/Cigarettes Smoking (n=20)	1.05	0.08	0.88 – 1.2	
Drinking with Reverse Smoking (n=06)	1.33	0.15	1.02 – 1.6	
Drinking with Tobacco Chewing (n=26)	1.2	0.07	1.04 – 1.3	
Drinking only (n=2)	1.0	0.27	0.46 – 1.5	<0.05
Non-Drinkers with Bidi/Cigarettes (n=13)	1.4	0.10	1.17 – 1.6	
Non-Drinkers with Reverse Smoking (n=13)	1.9	0.10	1.7 – 2.1	
Non-Drinkers with Tobacco chewing (n=19)	1.2	0.08	0.9 – 1.3	
Non-Drinkers with Non- smoker (n=24)	1.8	0.07	1.6 – 1.9	

All the habits were found to be correlated with the HNC patients. All these parameters shows significance with etiology of head and neck cancer ($p<0.05$). Smoking and drinking habits does not show any positive association with each other habits for anatomy of disease, where in two way ANOVA both smokers, drinkers, non smokers and non drinker does not show any variation in etiology of anatomy of the disease.($p>0.05$). Further correlation study was done for stage and grade of the disease with smokers and drinkers but it does not show any significance as the p value of stage and grade is greater than 0.05 ($p=>0.05$) (data not shown here).

DISCUSSION

Cancer of head and neck region constitute the third most common type of all cancers in males and females. Tobacco related cancers accounted for 34% of all cancers in males and 16% in females. In India, Head and Neck cancer found to be 30% of all cancers in males except Dibrugarh in Assam (49.6%) and in females it is 11 – 16%. Overall, 57.5% (males and females) of global head and neck cancers (excluding esophageal cancers) occur in Asia especially in India due to similar risk factors like cigarettes, beedis, cigars and reverse smoking (Chaturvedi, 2009). These malignancies are among the most debilitating and disfiguring of all cancers.

The overall scenario is fast changing with a reversal of the Male: Female ratio and is due to the increased use of tobacco and alcohol among women. Oral cancer most commonly occurs in middle and older aged individuals, although a striking number of these malignancies are also being documented in younger adults in recent years. The present prospective study was focused only on the confirmed diagnosis of squamous cell carcinoma of head and neck cancer patients. Out of 123 malignant patients, males and females accounts 61.78% and 38.21% respectively. 67.4% subjects belong to rural and 32.5% subjects belong to urban areas. Most of the rural people are settled in urban areas for livelihood. Majority of the subjects (40.65%) consists of labour (daily wage workers at various industries), 24.39 % females are housewives, 19.51% are from agricultural works where most of them exposed to pesticides and other environmental carcinogens. Only 15.44% patients are private employees. Occupational risk factor found to be significant with gender where p value is <0.05 in both males and females. Males are predominating in this study found to be more at risk than females due to various exposures which is similar to the study of (Md Salahuddin Siddiqui *et al*., 2012). Because exposure to tobacco and other carcinogens were far more common in "male jobs" than females in Indian scenario, the exposed men had mostly been occupational industrial

workers, daily wagers, agricultural workers and private jobs may develop various kinds of cancers including lung cancer (Kirmani *et al*., 2010). However, the exact mechanism and its correlation to confounding factors were not identified. Inadequate occupational safety standards, and insufficient enforcement; poor labelling of pesticides; illiteracy; and insufficient knowledge of pesticide hazards (Jocket *et al*., 1992) may contribute in occupational risk factors. Higher number of male incidence in the present study suggests that males often indulged into habits i.e. smoking, tobacco chewing, alcohol consumption and combination of these with occupational risk factors and other environmental carcinogens during the working time (Abdul Majeed Kavarodi and Mary Thomas, Johnny Kannampilly, 2014).

Smoking tobacco is associated with an increased risk of oral cavity and pharynx (Castellsagué *et al*., 2004; Negar Mafi *et al*., 2012; Satyanarayana and and Maha Devi, 1989) in head and neck cancer with risks increasing in a dose dependent fashion and declining with the duration of smoking cessation. It was proven in the present study that smoking contributed to head and neck cancer in both males and female with any form of tobacco exposure (Table 2) where p value <0.05. The exposure duration to tobacco and related products also increases the cancer incidences proportionally where p value is <0.05 (Table 3). Surprisingly incidence of head and neck cancers were rising in females day by day in India with the increased smoking and drinking habits as in males. Reverse smoking, tobacco chewing in coastal regions of Andhra pradesh and Orissa are very common in females. A recent study reveals that smoking, tobacco chewing, reverse smoking were contributing cancer risk in males and females increasing the incidence in female cases. In present study, the frequency of reverse smoking females is more than males. Similar findings were reported by (Satyanarayana and Maha Devi, 1989). As proven by many studies, alcohol consumption increases the risk of oral and pharyngeal cancers. In the present study also alcohol consumption shows a great impact on head and neck cancer, but this does not show any influence on the anatomic sites. Remarkably a study conducted in Puerto Rico shows no significant difference among tongue, other oral and pharyngeal cancers in both sexes in relation to alcohol consumption (Hayes *et al*., 1999). Pharyngeal cancers are more common in men which shows strong association with increased alcohol consumption (Blot *et al*., 1988) in US population. Conversely Franceschi *et al*., 1999 reported oral cancer associated with alcohol consumption is more common when compared with pharyngeal cancer in Italy and Switzerland population (Franceschi *et al*., 1999). Results regarding to anatomical sites with respect to drinking habits have varied from study to study. Report by Malcolm A Moore *et al*., 2009 described high numbers of pharyngeal and/or laryngeal cancer are also consistently observed in the more developed cities in South Asian countries including India (Malcolm and Moore, 2009). Hussain Gadelkarim Ahmed *et al*., 2012 showed that prevalence of HPV is high among Sudanese patients with head and neck cancers (HNC) other than above discussed risk factors (Hussain Gadelkarim Ahmed *et al*., 2012). No single study had adequate data to test the possible differences in alcohol-related risk across sub sites, and the apparent differences may be due to chance alone. Other than these risk factors genetic mutations plays major role in carcinogenesis of Head and Neck cancers includes EGFR mutations, but role of this widely studied gene also showed no association with oral cancers (Dhaval Tushar Mehta *et al*., 2014). One more significant finding in the present study is that the cancer patients having both habits or any one habit of drinking and smoking are at high risk when compared with the cancer patients who does not have any habit of drinking and smoking. Blot WJ *et al*., 1988 estimate that smoking and drinking combined account for about 75% of all OPC in the United States (Blot *et al*., 1988). A similar study by Varela-Lema *et al*., 2009 in a Spanish male population found that tobacco smoking was associated with OPC. In the present study, tobacco chewing and smoking were more elevated among men than women (Varela-Lema *et al*., 2009).

Same finding was stated by Addala *et al*., 2012, Md Salahuddin Siddiqui *et al*., 2014 and also reported in Iranian population (Addala *et al*., 2012; Md Salahuddin Siddiqui *et al*., 2014). As per previous literature incidence of head and neck cancer with smoking and alcohol consumption is extremely rare among women in southern India, while paan-tobacco chewing is commonly seen in women in coastal areas of Andhra Pradesh (Gajalakshmi *et al*., 2003), Telangana region (Padmavathy *et al*., 2010) in Andhra pradesh in contrast to the present study (Padmavathy *et al*., 2010). The study of Subapriya in 2007 shows that addiction of alcoholic drink and intake of tobacco in any form further increases the risk for oral cancer by eleven fold in Southern India which shows close association with this study. Religion, consanguinity, diet and marital status did not show any association with the development of head and neck cancer independently (Subapriya *et al*., 2007). Our data was also supported to results of Ramita Basu *et al*., 2008 data suggest that tobacco in both smoked and smokeless forms is the most important risk factor for both development and prognosis of HNSCCs.

Conclusion

From the results, it is clear that head and neck cancer incidences are increasing with personal habits like tobacco exposure and alcohol consumption. Reverse smoking and drinking habits predominates incidence of female head and neck cancer explained on the basis of available data. However, further studies needed to explain the details about quantity and frequency of alcohol usage, specific occupational exposure with duration, personal hygiene etc., with standardised questionnaire. In developing countries like India, it is utmost important to implement cancer control activities and has to be prioritized in order to make the country to reduce the burden of head and neck cancer to some extent. Proper counselling on tobacco cessation by the medical practitioners is required to protect against HNC.

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