

## Tobacco and Cancer: A Terrific Conditional Cross-Talk

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The exact history of tobacco use by human is still in dark. But, tobacco and its products have been used in two forms- smoked (combustible) and smokeless (non-combustible) tobacco. Pika (indigenously prepared hand-rolled bidi using a piece of leaf of kendu plant, *Diospyros melanoxylon*), bidi, cigarette, cigars and pipes etc are used as smoked items while khaini, snuff, gutkha, paan masala, betel quids (BQs) etc are used as non-smoked items. According to World Health Organizations, due to tobacco epidemic more than 8 million people are being killed in a year globally. It has also been estimated that more than 7 million of those deaths are due to direct tobacco use while around 1.2 million death cases are the result of non-smokers being exposed to second-hand smoke (SHS) [1]. Epidemiological studies have shown that there is an indomitable nexus between tobacco and cancer. Age, gender and economic status of the tobacco users, type and quantity of tobacco and above all frequency of tobacco use are some of the important conditions involved in the terrific cross-talk between tobacco and cancer.

Earlier, tobacco use was confined to the older section of the community. Males were predominantly used to consume tobacco in the form of either khaini/snuff or pika/bidi usually after the breakfast and launch in the community. Number of female tobacco users was very less and smoking cases among female were rare and confined to the rich and elite section of the community, Later on, towards the last decades of 20<sup>th</sup> century the young-adults were used to consume tobacco recklessly. Well packed, ready to use, branded khaini, gutkha, paan masala and cigarettes became the essential commodities of the young-adults in their day-to-day life. They accepted chewing and smoking of tobacco as part and parcel of their modern lifestyle. Growing incidence of tobacco related

cancer (TRC) among the young-adults has been observed to be in an alarming state. In spite of statutory warning, the trends of tobacco use has now spreaded to the school-going children community. Reports from across the world on TRC among the children are now become a highly sensitive issue and burning topic of discussion. Tobacco (khaini, gutkha, paan masala and cigarettes) pouches inside the pockets of children have raised a new quest among the parents, teachers and policy makers, so far as quality of life and future of the children are concerned.

Now, few questions related to tobacco use are- what is there in the tobacco which attracts the children, the young-adults and the old ones? Why do the tobacco users become careless on his/her health and quality of life? Why do the tobacco users knowingly ignore the statutory warning and opt for suffering? The only answer to many such questions is "Nicotine". Nicotine is one of the chief components of tobacco, naturally exists in the tobacco plants (*Nicotiana tabacum*). It is an alkaloid and an excellent stimulant that stimulates the addicts more and more. It is most readily absorbed by the oral mucosa when a tobacco product is chewed, inhaled, or smoked and rush into the nervous system via bloodstream. It triggers the release of dopamine- a type of neurotransmitter and is primarily associated with feelings of goodness and pleasure. Hyperactivity of dopamine leads to neuro-behavioural disorder called attention-deficit-hyperactivity disorder (ADHD) among children. Children with ADHD may have trouble in paying attention, imparting aggression and controlling impulsive behaviours. In most of cases, ADHD persists in adulthood and the victims easily go for gambling and illicit practice of addiction. As a nerve stimulant, it is very similar to those of cocaine and amphetamines. Nicotine is

5-10 times more potent than cocaine or morphine, 10-100 times more potent than barbiturates and thousand times more potent than alcohol in its addictive potential. While nicotine alone is a highly addictive substance, many chemicals are added to make tobacco more appealing and more addictive. That's why the tobacco users (irrespective of age and sex) are being attracted towards tobacco and fall in the tobacco-trap.

Active smokers smoke regularly and exhaust huge amount of smoke to the environment. Chain smokers may consume at least 56-60 bidi or cigarettes per day. Over four thousands chemical compounds are detected in the tobacco smoke. Most of these chemicals are known to be highly genotoxic, mutagenic and carcinogenic. Tobacco smoke contains nearly 400 to 500 gases, including carbon monoxide, ammonia, formaldehyde, hydrogen cyanide and dimethyl-nitrosamine and are known to be potential candidates for patho-physiological disorders. Tar- a sticky, black coloured substance in tobacco smoke contains many known carcinogens including tobacco specific N-nitrosamines (TSNA), aromatic hydrocarbons, heavy metals such as lead, chromium and cadmium as well as radioactive substance Polonium-210 [2,3]. All these chemicals directly hit the mucosa of oral cavity and the lungs in particular. Few more questions related to passive or second hand smoking (SHS) are really curious. Is passive smoking hazardous for health? Can it be a cause of lung cancer or any other type of cancers? Is it possible to avoid the SHS? Can it be prevented? Inhaling of litting out and breathing out of smoke of active smoker by the near and dear one is called passive or second hand smoking and the inhalers are considered as passive or second hand smokers. Numerically, an active smoker forced to create a number of passive smokers, if someone smokes at any public place. All the members in a family are frequently exposed to the second hand smoke of a single active smoker. Recent evidences indicate that passive smoking induces lymphoma, leukaemia and myeloma in children while cancer of lungs, breast and heart diseases among adults. Pregnant women exposed to passive smoke are more prone to premature birth and their baby is more at risk of low birth-weight and sudden infant death syndrome (SIDS) or cot death [4]. Reverse smoking is a unique kind of smoking where the burnt end of the hand rolled bidi or cigar is kept inside the oral cavity. In addition to smoke, heat generated from the lit-end of the bidi or cigar directly affect the palate- the roof of the oral cavity. Smoke-bathed thermogenic palatal cancer is a common feature among the reverse smokers. Reverse

smoking is being commonly practised among the tribal people of Andhra Pradesh and Telengana states of India [5].

Recently developed Electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS), commonly called as electronic cigarettes or e-cigarettes are granted as modern gift for the smokers, Toxic effect of e-cigarettes have also been evaluated. In order to make a safer alternative to regular cigarettes, these are designed to deliver either nicotine or non-nicotine aerosol through inhalation without combustion of tobacco, but by burning a solution of propylene glycol, with or without glycerol, and flavouring agents [6]. A report on multi-cohort longitudinal study showed that the adolescent vapers were preferred to use of nicotine-free e-cigarettes in Norway. On the other hand, nicotine vapers were more likely to use other tobacco products and were observed to have conduct problems and symptoms of depression compared to nicotine-free vapers [7]. In an investigation, Goniewicz., *et al.* have found that the e-cigarette vapours are not free from toxic substances. But, the levels of the toxicants in the e-cigarette vapours were 9 fold to 450 fold lower than the cigarette smoke and in many cases, trace amount of toxic substances were also detected [8]. Use of e-cigarettes by children and adolescents is highly risky. It increases the risk of cardio-vascular diseases and lung disorders.

Chewing of tobacco and paan masala lead to direct contact with the oral mucosa. Chemical constituents of smokeless tobacco are nicotine, nitrosamines, polycyclic aromatic hydrocarbons (PAHs), benzo-a-pyrene (BaP), formaldehyde and a number of heavy metals not only mix with saliva but also seriously affect physiology of salivary glands. A number of carcinogens, such as, tobacco-specific nitrosamines (TSNAs), N-nitrosornicotine (NNN), 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanabasine (NAB), volatile nitrosamines N-nitroso-dimethylamine and N-nitrosodiethylamine, have been detected in the saliva of betel quid and tobacco chewers [9,10]. Due to chewing of tobacco, gutkha, paan masala, BQs and snuff dipping, the observed immediate effects are pyorrhea, halitosis (bad breath), gingivitis, periodontitis, psoriasis, fibrosis and sores in the oral cavity. On long term-effects, the victim may suffer from leukoplakia, erythroplakia, erythro-leukoplakia, cancer of the lips, tongue, gingiva, floor of mouth, palate, cheeks and upper aero-digestive tract. Not only that, use of smokeless tobacco has also been associated with cardiovascular risk, metabolic disorders and sexual dysfunction in both sexes. Li

and Sheih reported that independent and combined impact of BQs chewing with cigarette smoking and alcohol drinking increase the risk of salivary gland tumor [11].

The epidemic of tobacco use is one of the greatest threats to the public health. Due to unrestricted and increased demand as well as illicit supply of tobacco globally, a pathetic and panic picture of global health will be well visualized in the near future. Use of tobacco is a primary cause of many oral diseases and affects quality of life. Prolonged use of tobacco induces oral cancer, lung cancer, periodontal diseases, and even congenital defects in children whose mothers smoke during pregnancy. Smoking of tobacco has also been linked to the development of cancers of the stomach, colorectum, pancreas, kidney, prostate, uterus, cervix, ovary and leukaemia.

In fact, genotoxicity of tobacco seriously affects the DNA-the molecular signature and instruction manual of the cell. As a result, the affected cell becomes abnormal, uncontrolled and turned into a cancerous one. The carcinogens of the tobacco inactivate the tumour suppressor genes (TSGs) and activate the inactivated proto-oncogenes to oncogenes. Carcinogenic effects of tobacco, thus, trigger cellular entropy and anarchy. Anarchism of mutated cell initiates oncogenesis. Ultimately, growth of neoplasms takes place irrespective of oral sites and sex. Chewing and smoking of tobacco lead to differential expression of keratin in a number of cytological atypias including micronucleated cells (MNCs) in the oral mucosa. Formation of micronuclei in the oral mucosal cells is considered as an end point of either chromosomal damage or segregation errors during mitotic cell division. Appearance of micronuclei in oral mucosa reflects a genotoxic or carcinogenic exposure. Longer the period of tobacco consumption, more is the frequency of MNCs in the oral mucosa. Mohanta, *et al.* have reported that increased frequency of MNCs from normal to precancerous to cancerous groups with respect to increased age groups in both sexes is a fact [12]. Bhat, *et al.* demonstrated alterations in miRNA expression in oral keratinocytes in response to chewing and smoking of tobacco. Significant upregulation of miR-31-5p was observed by them in OKF6/TERT1-Tobacco cells. They have also observed that miR-29c-3p and miR-146a-5p were over-expressed in chewing tobacco treated cells, whereas miR-1266-5p and miR-196b-5p were downregulated in oral keratinocytes chronically treated with tobacco [13].

Both smoked and all forms of smokeless tobacco induce cancer. None is a safe way to use tobacco. Passive smoking is no less, but equally hazardous to the health of second hand or passive smokers. Tobacco is a slow poison. It kills and triggers premature and unnatural death. Therefore, the addicted individuals must aware of their health-wealth and to improve their quality of life. Neither more taxation nor ban on tobacco use can control the tobacco consumption. It may promote illicit tobacco business, which can not be ignored. Only self consciousness of the individual followed by public awareness to quit tobacco can not only be helpful to dismantle the ongoing "terrific conditional cross-talk" between tobacco and cancer but also be helpful to make a tobacco-free world. Therefore, research-based curriculum should be designed and be implemented from primary to post-graduate level in this regard. Thinkers, social workers, Government and Non-Government agencies must come forward to formulate policies on Tobacco Related Cancer free World.

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