Review Article

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Potential health impacts and lung microbiome changes among smoking and smokeless tobacco use : A technical scan

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Abstract:

Globally, 1.3 billion peoples use tobacco products daily, most of them from low- and middle-income countries. Every year, 8 million of the population died because of the usage of tobacco, as per the WHO report. Tobacco-related diseases, likely lung cancer, emphysema chronic obstructive pulmonary disease, and chronic respiratory diseases, are more common. Nicotine is a highly addictive chemical found in the tobacco plant and also in all other tobacco products. All tobacco products contain nicotine that causes the release of dopamine in the pleasure and motivation areas of the brain. Both smoking and smokeless tobacco products contain many harmful chemicals that affect the lung mucociliary clearance and also inactivate the immune system and lead to increases in the risk of infection and the development of deleterious bacterial growth in the lungs. In the lung microbiome, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa* bacterial species were found to a higher level in smoking tobacco users as that may increase morbidity and mortality. The lung microbiome changes taking place in the lung due to smokeless tobacco usage are less documented so far. In future research, microbiome studies help to understand disease pathogenesis.

Keywords:

Bacterial growth, inflammatory changes, tobacco users

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Introduction

Globally, every year, 8 million of the population died because of the usage of tobacco, as per the WHO report. Around 7 million populations died because of the direct use of tobacco and nearly 1 million population died indirectly by secondhand smoke.[1] In India, tobacco kills more than 1 million people every year.[2] India is the second-largest population of tobacco users in the world. Different forms of tobacco products are available in India. Tobaccos in smoking and smokeless products are injurious to health. Tobacco users are associated with noncommunicable diseases like ischemic heart diseases, cancers, chronic respiratory diseases like chronic obstructive pulmonary disease (COPD), emphysema, and bronchitis which are leading causes of death globally.[3] Tobacco smoke contains 7000 chemicals, in

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which 69 chemicals are related to cancer and many are identified as toxic substances.[4] Smokeless tobacco contains nearly 4000 chemicals, in which 30 or more chemicals are prone to cause cancer. In smokeless tobacco products, some of the chemicals are as same as present in cigarette smoke. Tobacco users are at more risk of developing diseases reason being addicted to nicotine, lack of awareness of risk, and difficulty in quitting. Nicotine is a highly addictive chemical found in the tobacco plant and also in all other tobacco products.[5] Nicotine causes addiction and forces people to use tobacco products. Tobacco smokers are directly affected in the lung in higher concentrations than any other system in the body. The effects of smoking will lead to impairment of the protective mechanisms in the lungs, which increases the risk of infection and lung destruction. In a healthy human, lung microbiome studies are published, in which *Proteobacteria*, *Firmicutes*, and *Bacteroidetes* are most commonly present at the phylum level. At the genus level, *Pseudomonas*, *Streptococcus*, *Prevotella, Fusobacteria,* and *Veillonella* predominates and the contributions from potential pathogens including *Haemophilu*s and *Neisseria* were found very less.[6] The lung microbiome changes taking place in the lung due to smokeless tobacco usage are less documented, especially in India. With this background, this review paper will give you an overview of the effects of tobacco users (both smoking and smokeless) and its health impacts along with immunological changes pertaining to bacterial growth in the respiratory system.

Health Problems Due to Smokeless Tobacco Use

Smokeless tobacco products include dip, chew, spit, oral, and spitless tobacco and dry and moist snuff. It is addictive like cigarette smoking. One can of snuff contains the same quantity of nicotine as four packs of cigarettes.[7] Dipping 8–10 times a day is equivalent to smoking 30–40 cigarettes per day. Nicotine stays in the bloodstream longer with smokeless tobacco when compared to cigarettes. Oral tobacco contains 30 chemicals known to cause cancer. The most harmful of these are tobacco-specific nitrosamines, which are known to identify lung cancer.[7]

Smokeless tobacco users have more chances to get several diseases like cancers, oral diseases, cardiovascular diseases, stroke, and increases risk during pregnancy.[8,9] which are listed in Table 1.

Health Problems Due to Smoking Tobacco Use

Tobacco smoking includes cigarettes, bidis, cigars, cheroots, rolled cigarettes, tobacco rolled in maize leaf and newspaper, hookah, pipes, chillum, and chutta.[2] Cigarettes and bidis are more commonly used in India.[3]

Smoking tobacco users had strong relation and more incidents of respiratory diseases, cancers, cardiovascular diseases, stroke, pregnancy-related issue and other diseases like Rheumatoid arthritis, kidney damage, eye diseases such as age-related macular degeneration, dental disease like caries, diabetes, inflammatory bowel diseases, and erectile dysfunction are more common among smoking tobacco users[10-12] which are listed in Table 1.

Health Impacts Due to Passive Smoking

Passive smoking increases the risk of respiratory illness, including COPD and reduced lung function. An incident of cancer such as the throat, chest, breast, and larynx has occurred in passive smokers.

The summary of health impacts due to smoking and smokeless tobacco users is listed in Table 1.

Hazards of Tobacco Compounds

Tobacco smoking directly exposes the epithelial tissue to at least 60 powerful chemical carcinogens with the potential to cause DNA damage to the larynx, bronchi, and epithelial cells by the contents of tobacco smoke such as nicotine, tar, formaldehyde, ammonia, carbon monoxide, benzopyrenes, acetone, hydroxyquinone, cadmium and nitrogen oxides, and carbon dioxide.[13]

Nicotine is the major reason for the predominant behavioral effects of tobacco. Nicotine interacts with the nicotinic acetylcholine receptors and stimulates dopaminergic transmission. This stimulates the reward center and is responsible for mood elevation and improvement in cognitive function.[14]

Exposure to nicotine stimulates the adrenal glands and release adrenaline. There is an immediate release of glucose, as well as an increase in heart rate, breathing activity, and blood pressure.[15]

Carbon monoxide molecules attach to the hemoglobin of the red blood cells and reduce the transportation of oxygen to the tissue lead to hypoxia where there is a reduction in the count of red blood cells in the blood.[16]

Tar is a sticky substance that contains benzopyrene, which is one of the deadliest cancer-causing agents. Compounds such as carbon dioxide, nitrogen oxides, volatile nitrosamines, hydrogen cyanide, ammonia volatile sulfur-containing compounds, alcohols, aldehydes, benzene, volatile hydrocarbons, and ketones

Table 1: Health impacts due to smoking and smokeless tobacco users

Health impacts due to smoking tobacco use	Health impacts due to smokeless tobacco use
Cancer - lung, gastrointestinal tract, liver, pancreas, kidney, urinary bladder, oral cavity, nasal cavity, and neck	Cancers - mouth, throat, esophagus, stomach, pancreas
Respiratory diseases - COPD, chronic bronchitis, emphysema, asthma, and tuberculosis	Leukoplakia
Cardiovascular diseases	Gum diseases
Stroke	Tooth decay
Rheumatoid arthritis	Tooth lose
Kidney damage	Stained teeth
Eye disease: age-related macular degeneration	Early delivery in pregnancy
Dental disease like caries	Heart attacks
Diabetes	Stroke
Inflammatory bowel diseases	Nicotine poisoning in children
Erectile dysfunction	
Pregnancy-related diseases-early delivery, death of the baby before birth, low birth weight, sudden infant death syndrome, and ectopic pregnancy	

COPD: Chronic obstructive pulmonary disease

are known to cause cancers in multiple organs of the body. This tar sticks inside the mouth, pharynx, trachea, and bronchial tubes.[3]

Irritants

Acetone, phenols, and hydrocyanic acid are all irritants that can attack the walls of the bronchi, the nose, and the eyes. Hydrocyanic acid, more commonly known as prussic acid, is one of the most toxic products found in tobacco smoke.[16]

Pathogenesis of Diseases Induced by Tobacco Smoking

In normal lungs, more than 10 μm nanoparticles expel by ciliary actions, but tobacco particles <2–10 μm get to attach to the walls of the bronchi as the airflow slows in the smaller passages.[17] Cigarette smoke inhaled particles and pathogens are recognized by pattern recognition receptors (PRRs) on the plasma membrane of the alveolar epithelial cells and macrophages. There are different types of PRRs such as toll-like receptors, cytosolic nucleotide oligomerization domain-like receptors (NLRs), and RIG-I-like receptors. PRRs are also activated during damage-associated molecular patterns released after tissue damage, resulting in the production of inflammatory cytokines. NLRP3 inflammasome promotes the secretion of interleukin (IL)-1α, IL-1 β, IL-33, and IL-18. The induced IL-1 β and IL-18 activate neutrophils, macrophages, and helper T (Th) 1 and Th17 lymphocytes resulting in type 1 airway inflammation. Inflammasome-dependent cytokines are involved in COPD pathogenesis.[18]

Alveolar macrophages and neutrophils release proteases, like matrix metalloproteinases (MMPs) and neutrophil elastase (NE), which cause elastin degradation that results in alveolar wall destruction. Alveolar macrophages play a main role in airway inflammation. These cells secrete multiple chemokines and cytokines, such as tumor necrosis factor-α, that stimulate the expression of adhesion molecules on endothelial cells and make action to the migrating of various inflammatory cells. Alveolar macrophages produce reactive-oxygen species (ROS), metalloproteinases (MMPs), and cathepsins to interrupt alveolar structures and induce epithelial fibrosis mediators such as TGF-β1 to trigger airway change.[19]

The neutrophil is an important component of type 1 inflammation. Elevated neutrophil levels in sputum are associated with COPD severity. Neutrophil migration to the lungs is stimulated by the accumulation of ROS-induced-phosphatidylinositol 3,4,5-triphosphate at the injury site. Besides, chemokine C-X-C motif ligand (CXCL) 1, CXCL8, and leukotriene B4 produced by macrophages and IL-22, IL-17A produced by Th, lymphocytes, and innate lymphoid cell 3 are involved in the determination of neutrophil motility. Airway neutrophils secrete that myeloperoxidase, NE, cathepsins, proteinase, and metalloproteinases (MMPs) destroy alveoli and promote mucus production in the submucosal glands and goblet cells.[20]

Antigens released by cell and tissue damage are recognized by the dendritic cells and presented to T-lymphocytes and activate adaptive immunity. Cigarette smoke-induced neutrophil extracellular traps can enhance plasmacytoid dendritic cells, generating naive CD4-positive T-cells into Th1 and Th17.[21] CD8+ cytotoxic T-lymphocytes and CD4+ Th1-lymphocytes as well as natural killer cells comprise the innate immunity and release perforin and granzyme B to induce apoptosis of the epithelial cells, followed by alveolar destruction. This is the pathogenesis of emphysema and COPD.[22]

Table 2: Global and Indian studies on microbiome changes related to tobacco users

Title of the study	Author	Study place	Journal and year of publication	Result
Cigarette Smoke Exposure Impairs Pulmonary Bacterial Clearance and Alveolar Macrophage Complement-Mediated Phagocytosis of *Streptococcus pneumonia*	Phipps JC *et al*.	The University of Michigan. America[28]	Infection and Immunity 2010	In mice, cigarette smoke exposure increases the risk of pneumococcal pneumonia and also increased IL-1, IL-6, IL-10, and TNF-α
Cigarette Smoke Exposure Exacerbates Lung Inflammation and Compromises Immunity to Bacterial Infection	Lugade AA *et al*.	Roswell Park Cancer Institute, USA[29]	The Journal of Immunology 2014	In mice, cigarette smoke exposure has decreased the effect on the generation of adaptive immune responses to NTHI. Cigarette smoke reduces levels of IFN-alpha, IL-4, and B-cells
Molecular Determinants of the Pathogenesis of Disease Due to Non-Typable *Haemophilus influenzae*	Rao VK *et al*.	Washington[30]	FEMS Microbiology Reviews 1999	*Haemophilus influenzae* is located mainly in the oro- and nasopharynx. It colonizes 40%-80% of healthy individuals, with a frequency of carriage that is higher in children than in adults
Impact of Cigarette Smoke on Clearance and Inflammation After *Pseudomonas aeruginosa* Infection	Drannik AG *et al*.	Canada[31]	American Journal of Respiratory and Critical Care Medicine 2004	In mice, *P. aeruginosa* is a pathogen that is frequently isolated from pneumonia patients. Exposure to cigarette smoke increases inflammation and decreases the clearance of *P. aeruginosa*
Induced Sputum microbiome in Smoker and Nonsmoker COPD Subjects and its Association with Lung Function in Indian Subjects	Ghosh B *et al*.	India[32]	European Respiratory Journal 2017	*Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria* and *Fusobacteria* were the moret common phylum level in smokers. Phylum *Proteobacteria*, which includes many pathogens showed higher level in COPD subjects
Tobacco use Increases Susceptibility to Bacterial Infection	Bagaitkar J *et al*.	USA[26]	Tobacco Induced Diseases (2008)	Smokers are at high risk of respiratory infection by several bacterial pathogens, including *S. pneumonia, N. meningitidis, H. influenzae*, and *L. pneumophila* nasopharyngeal microflora of smokers contains fewer normal bacteria such as α-hemolytic and nonhemolytic streptococci, and *Prevotella* and *Peptostreptococcus species* that can interfere with colonization by selected pathogens *S. pneumoniae*, *H. influenzae M. catarrhalis*, and *Streptococcus pyrogens* and that the nasopharyngeal microflora also contains more potential pathogens compared with those of nonsmokers
Impact of Cigarette Smoke Exposure on Host-Bacterial Pathogen Interactions	Garmendia J *et al*.	A review paper[33]	European Respiratory Journal 2012	Microorganisms isolated from the lower respiratory tract of smokers and of persistently colonized patients are nontypeable *Haemophilus influenzae* (NTHi), M. catarrhalis, *S. pneumoniae*, and *P. aeruginosa*. This pathogen is responsible for COPD
Cigarette Smoke Extract Modulates *Pseudomonas aeruginosa* Bacterial Load Via USP25/HDAC11 Axis in Lung Epithelial Cells	Long C, Lai Y *et al*.	USA[34]	American Journal of Physiology-Lung Cellular and Molecular Physiology 2020	Cigarette smoke extract downregulated USP25/HDAC11 axis which increases the bacterial load of *P. aeruginosa* in lung epithelial cells
Effects of Smoking on the Lower Respiratory Tract Microbiome in Mice	Zhang *et al*.	China[35]	Respirotary Research 2018	Smoking has increased the risk of inflammation and also altered microbial diversities and communities in the lower respiratory tract of mice
Comparison of the Respiratory Microbiome in Healthy Nonsmokers and Smokers	Alison Morris *et al*.	USA[36]	American Journal of Respiratory and Critical Care Medicine 2013	*Enterobacteriaceae*, *Haemophilus*, *Methylobacterium*, *Tropheryma*, and *Ralstonia* species are found in the lungs. *Porphyromonas*, *Neisseria*, and *Gemella* were found in oral community compare smokers and nonsmokers
Characterization of Bacterial Communities in Selected Smokeless Tobacco Products Using 16S rDNA Analysis	Stephen B Stanfill *et al*.	USA[37]	PloS One 2016	US-based dry snuff products analysis *Actinobacteria*, *Firmicutes, Proteobacteria*, and *Bacteroidetes* were identified. Moist snuff products were more by *Firmicutes*. Toombak samples contained mostly *Actinobacteria* and *Firmicutes* (*Aerococcaceae*, *Enterococcaceae*, and *Staphylococcaceae*) were identified

Contd...

Table 2: Contd...

Title of the study	Author	Study place	Journal and year of publication	Result
Metagenomic Analysis of Bacterial Species in the Tongue Microbiome of Current and Never Smokers	Noriaki Sato *et al*.	Japan[38]	Npj Biofilms and Microbiomes (2020)	In smoker oral microbiome single-nucleotide variant profiles of *A. graevenitzii, M. micronuciformis, R. mucilaginosa, V. dispar*, and one *Veillonella* spp. were significantly different between never and current smokers
A Case Study of Salivary Microbiome in Smokers and Non Smokers in Hungary: Analysis by Shotgun Metagenome Sequencing	Roland Wirth *et al*.	Hungary[39]	Journal of Oral Microbiology (2020)	*Prevotella, Veillonella*, and *Streptococcus* were the predominant genera in the saliva in smoker and nonsmokers smoking-associated dysbiosis of the salivary microbiome in current cigarette smokers, especially increased abundance of *Prevotella* and *Megasphaera* genera, may facilitate disease development

TNF-α: Tumor necrosis factor-alpha, NTHI: Nontypeable *Haemophilus influenza*, IFN: Interferon, IL: Interleukin, COPD: Chronic obstructive pulmonary disease, USP: Ubiquitin-specific peptidase, HDAC: Histone deacetylase, rDNA: Recombinant deoxyribonucleic acid, *P. aeruginosa: Pseudomonas aeruginosa, S. pneumonia: Streptococcus pneumonia, N. meningitides: Neisseria meningitides, H. influenza: Haemophilus influenza, Legionella pneumophila: Legionella pneumophila, Moraxella catarrhalis: Moraxella catarrhalis, A. graevenitzii: Actinomyces graevenitzii, M. micronuciformis: Megasphaera micronuciformis, R. mucilaginosa: Rothia mucilaginosa, V. dispar: Veillonella dispar*

Tobacco Smoke Induces Bacterial Infection

Tobacco smoke plays a direct role in bacterial colonization of the respiratory tract by impairment of mucociliary clearance of bacteria. Nicotine plays a role in the impairment of mucociliary clearance. Tobacco smoke is capable of affecting neutrophils and monocytes function both directly and indirectly. Neutrophils, monocytes, macrophages, and dendritic cells are compromised by tobacco smoke. Tobacco smoke compromises the antibacterial function of white blood cells, including neutrophils, monocytes, T–cells, and B-cells also increase bacterial infection.[23-25]

Tobacco exposure suppresses general responsiveness to bacteria and lipopolysaccharide reflected in a downregulation of surface pathogen recognition receptors (TLR-2 and MARCO) with reduced phagocytic, ROS generating and bacterial killing capacities. Dendritic cells, whose primary function is to process antigens and present them to adaptive immune cells, thus bridging innate and adaptive immune responses, are also negatively influenced by tobacco smoke and smoke constituents.[26,27]

In tobacco users, bacterial species such as *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa* were found higher level in lungs, especially in smoking tobacco users. This may increase the susceptibility to certain diseases such a emphysema, COPD, and pneumonia. A list of some global and Indian studies published in this context is explained in Table 2.

Conclusion

This review concludes that tobacco products are injurious to health. Tobacco kills millions of people globally and tobacco usage leads to several diseases. Thousands of harmful chemical contents present in the tobacco product affecting the health. Nicotine acts as an addictive substance combined with other chemicals that reduce the innate immune function, mainly impairment of mucociliary defense in the lungs. This causes a high risk of developing deleterious growth of bacteria species like *S. pneumoniae, H. influenzae, M. catarrhalis,* and *P. aeruginosa* that may increase the morbidity and mortality. Impacts of smoking and smokeless tobacco products on lung microbiome are not well-documented in India, especially in South India. Further studies are needed to establish the relationship between tobacco usage and its impacts on lung function and microbiome which may be helpful to create a policy guideline regarding treatment of such diseases and also to create an awareness among the users.

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Conflicts of interest
There are no conflicts of interest.

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