E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/15.1.233

Research Article

Mechanistic Insights into Oxidative Damage and Chronic Inflammation

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Received: 20.04.25, Revised: 2.05.25, Accepted: 26.06.25

ABSTRACT
Smokeless tobacco (ST) products play leading roles in the aetiology of oral cancer in human beings following mechanisms that include oxidative stress, chronic inflammation and microbial dysbiosis within the oral cavity. This review summarizes the existing studies in terms of how carcinogens contained in ST, which include tobacco-specific nitrosamines (TSNAs) andpolycyclic aromatic hydrocarbons (PAHs), cause production of reactive oxygen species (ROS), damaged DNA, and genome instability. Moreover, the exposure to ST induces prolonged stimulation of proinflammatory cytokines and transcription factors that promotes a pro-tumorigenic microenvironment. Another question the review deals with is the changes in the oral microbiome due to the ST use which creates conditions where pathogenic species develop and play the role in the carcinogenesis. The insight of these complex molecular pathways is important to devise specific therapy plans, such as administration of antioxidants and antiinflammatory compounds, to reduce the risk of oral cancer associated with ST.

INTRODUCTION

Oral cancer is a serious health burden affecting different countries throughout the world and the use of smokeless tobacco (ST) is a major etiologic factor in the countries where it is widely used. ST products are not combusted as smoked tobacco and instead are applied in the mouth, but they provide an unprecedented exposure of oral mucosa to a complex mixture of carcinogens. A multi-faceted process is involved in which the long-term exposure to the said substances induces and facilitates the malignant transformation of the oral cells.

The majority of individuals view smokeless tobacco products as a primary factor in the development of oral cancer in humans. The use of ST products, such as chewing tobacco, snuff, and naswar, has been associated with an increased risk of oral cancer, particularly in South Asian countries (Asthana et al. , 2018). Oral cancer poses a significant public health challenge because it has a significant impact on mortality and morbidity globally. Repeated studies have demonstrated a link between ST consumption and oral cancer; evidence suggests that ST products contain carcinogenic chemicals such tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs), which can induce oxidative stress, chronic inflammation, and microbial dysbiosis in the oral cavity (Rodu, 2004). The development of oral cancer linked to ST is based on complicated interactions between genetic and environmental variables. ST usage has been shown to continuously stimulate proinflammatory cytokines and transcription factors, thereby establishing a protumorigenic microenvironment. Furthermore, ST exposure can alter the oral microbiome, encouraging the growth of harmful bacteria that support carcinogenesis (Sarkar et al. (2023)).

The purpose of this review is to thoroughly analyze the mechanistic evidence about how ST causes oral cancer through changes in the oral microbiome, persistent inflammation, and oxidative damage. We will be able to understand the nature of the illness progression and identify the treatment one as well as the potential prophylactic strategy through these mechanisms.

LITERATURE REVIEW

Various Smokeless tobacco (ST) such as chewing tobacco, snuff, and betel quid have numerous cancer causing substances which trigger oral cancer development inducing oxidative stress and maintaining an inflammatory state (IARC, 2012). The various mechanisms that occur among oral cancer development due to ST exposure involve release of reactive oxygen species and repair of the damage done on the DNA as well as

sustained inflammatory reactions (Caliri et al., 2021). As well as heavy metal (cadmium, arsenic, etc.), ST contains dangerous substances (tobacco-specific nitrosamines (TSNA), polycyclic aromatic hydrocarbons (PAHs), etc. that stimulate the production of ROS (Stepanov et al., 2010). The cellular macromolecules lipids, proteins and DNA undergo damage through oxidative processes, which superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-) carry out at ROS (Caliri et al., 2021).

The activation of NADPH oxidase (NOX) enzymes following nicotine and its metabolites intake leads to extra ROS formation according to studies (Kim et al., 2014). ROS production passes beyond the protection capacity of endogenous antioxidants SOD, CAT, and GPx which results in damaged DNA (Cao et al., 2016). Persistent oxidative stress causes DNA lesions, which include 8oxo2'deoxyguanosine (8oxodG), as this specific DNA lesion stands as a well-established biomarker in studies regarding oxidative DNA damage (Valavanidis et al., 2009). These DNA lesions trigger tumor suppressor gene mutations in TP53 and oncogene mutations in KRAS, which result in malignant cell development (Brown et al., 2019). The chemical compounds known as ST disrupt both base excision repair (BER) and nucleotide excision repair (NER) DNA repair pathways, which results in enhanced genomic instability (Cao et al., 2016). The chronic exposure to ST inhibits DNA repair enzymes OGG1 (8oxoguanine glycosylase) alongside other essential enzymes, which ultimately raises cancer formation risk (Shen et al., 2002).

The development of oral cancer due to ST becomes chronic inflammation when the proinflammatory cytokines TNFα, IL6, IL1β and transcription factors NFκB and STAT3 remain persistently activated (Kadam et al., 2021). The tumor progression occurs because these mediators drive cell proliferation while enabling angiogenesis and stopping apoptosis (Meng et al., 2022). Tumor development and immune evasion get enhanced by ST-induced inflammation that increases cyclooxygenase2 (COX2) expression to produce more prostaglandin E2 (PGE_2) (Wang and Dubois, 2010). Research indicates that the elevated expression levels of COX2 occur frequently in oral leukoplakia and squamous cell carcinoma (OSCC), thus demonstrating COX2's role in malignant cell transformations (St Guily et al., 2017).

Structural tobacco use leads to microbial imbalance by decreasing Streptococcus salivarius and raising pathogenic species like Porphyromonas gingivalis and Fusobacterium nucleatum (Kakabadze et al., 2020). The dysbiosis between bacteria releases lipopolysaccharides and other bacterial endotoxins that activate TOLL-like receptors (TLRs), which trigger NFκB signaling (Zhang et al., 2019). Some bacteria transform ST agents into carcinogenic metabolites, including acetaldehyde, that work together with ST chemicals to destroy DNA (Kadam et al., 2021). Tumor cell survival, together with invasion and metastasis, gets enhanced in this inflammatory reaction microenvironment (Meng et al.., 2022).

The combination of oxidative stress with inflammatory responses sustains themselves at higher levels as they drive ST-induced oral carcinogenesis. ROS activate NFκB and MAPK pathways through which they boost the production of proinflammatory cytokines (Caliri et al., 2021). Tissue damage and malignant transformation develop through a destructive cycle because inflammatory cells (neutrophils and macrophages) generate extra ROS (Brown et al., 2019). The united action between these factors leads to upregulated transcription factors such as Snail, Twist, and ZEB1, which drive the essential cancer metastasis mechanism known as EMT (Meng et al., 2022). The process of EMT enables tumor cells to spread into nearby tissues, which leads to unfavorable outcomes in patients diagnosed with OSCC (Smith et al., 2013).

The development of oral cancer from ST exposure relies on three main factors: oxidative DNA damage and chronic inflammation, and disturbances in the microbial composition of the mouth. Genomic instability develops because of ROS generation along with faulty DNA repair mechanisms, yet persistent inflammation forms an environment favorable to tumor development. The knowledge of these molecular pathways needs to be fundamental for making targeted therapeutic progress, including antioxidants and anti-inflammatory agents to decrease ST-related oral cancer development.

METHODOLOGY

This paper is an in-depth literature review on oral cancer caused by smokeless tobacco among human beings. The reviewed studies included in this paper range between 2002 and 2022, which means that the study in this area has lasted two decades. A systematic search of

major databases (PubMed, Scopus, Web of Science) was conducted using relevant keywords (e.g., "smokeless tobacco," "oral cancer," "oxidative stress," "chronic inflammation," "microbial dysbiosis").

Inclusion Criteria: Studies were included if they Investigated the mechanisms underlying ST-associated oral cancer development and Examined the role of oxidative stress, chronic inflammation, or microbial dysbiosis in ST-induced oral carcinogenesis.

Exclusion Criteria: Were review articles or conference proceedings without primary data and did not specifically focus on ST-associated oral cancer.

CONCLUSION

Oxidative DNA damage and chronic inflammation and microbial composition of the mouth disturbances are the three key factors underpinning the development of oral cancer as a result of the ST exposure. The genomic instability takes place due to the activity of ROS and maladaptive DNA repair systems, but the presence of chronic inflammation creates an advantageous environment to promote the growth of tumor. These molecular pathways should be well known in order to be able to make specific advancements in therapeutic advances such as antioxidants, anti-inflammatory compounds to prevent the development of oral cancer that is associated with ST.

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