

The Response of the Tongue Epithelial on Cigarette Smoke Exposure as a Risk Factor for Oral Cancer Development

by Desiana Radithia

Submission date: 18-Apr-2023 02:56PM (UTC+0800)

Submission ID: 2068133303

File name: 12._s-0040-1721312.pdf (370.99K)

Word count: 4135

Character count: 22020



The Response of the Tongue Epithelial on Cigarette Smoke Exposure as a Risk Factor for Oral Cancer Development

Neken Prasetyaningtyas¹ Nabilah Azzahra Jatiatmaja¹ Desiana Radithia² Hening Tuti Hendarti²
 Adiaستی Endah Parmadiati² Priyo Hadi² Fatma Yasmin Mahdani² Diah Savitri Ernawati²
 Rosnah binti Zain³ Nurina Febriyanti Ayuningtyas²

¹Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia

²Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia

³Faculty of Dentistry, MAHSA University, Bandar Saujana Putra, Jenjarom Selangor, Malaysia

Address for correspondence Nurina Febriyanti Ayuningtyas, drg, Mkes, PhD, SpPM, Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya 60132, Indonesia (e-mail: nurina-ayu@fkg.unair.ac.id).

Eur J Dent 2021;15:320–324

Abstract

Objective The aim of this study is to analyze the tongue epithelial response to cigarette smoke exposure on a number of macrophages, lymphocytes, plasma cells, and matrix metalloproteinase 9 (MMP-9) expression to determine the risk factor of oral cancer development.

Materials and Methods Thirty *Rattus norvegicus* will be exposed to two kinds of cigarette smoke by a smoking pump for 4 and 8 weeks. The tongues were collected to analyze the number of macrophages, lymphocytes, and plasma cells with hematoxylin-eosin. The MMP-9 expression was similarly analyzed with immunohistochemical staining and then compared with the control group.

Results The number of macrophages, lymphocytes, and MMP-9 expression was higher in the 8-week cigarette smoke exposure compared to the 4-week cigarette smoke exposure and the control group ($p < 0.000$). The number of plasma cell did not differ in the 8-week cigarette smoke exposure from that of the control group ($p > 0.05$). The number of plasma cells in the tongue tissue during the 4-week cigarette smoke exposure was not determined.

Conclusion Cigarette smoke exposure induces the risk of oral cancer development as a result of an increase in the number of macrophages, lymphocytes, and MMP-9 expression in the tongue epithelial.

Keywords

- ▶ cigarette smoke
- ▶ lymphocytes
- ▶ macrophages
- ▶ MMP-9 expression
- ▶ tongue

Introduction

Health problems caused by cigarettes do not only affect active smokers but also passive smokers. Various studies have shown that passive smoking has the same health risks as active smoking. More than two-thirds of Indonesia's population has been exposed to cigarette smoke since birth. The highest occurrence of passive smoking is in children aged 5 to

19 years and in women of reproductive age between 15 and 49 years.¹ Smoking can cause 15 types of cancer, including oral precancerous and cancerous lesion. In Indonesia, cases of oral cancer range from 3 to 4% of all cancer cases, and the mortality rate reaches 2 to 3% of the total number of deaths due to malignancy.²⁻⁴

Tobacco use has become a big problem for health around the world. Tobacco products contain thousands of chemical

published online
December 7, 2020

DOI <https://doi.org/10.1055/s-0040-1721312>
ISSN 1305-7456.

© 2020. European Journal of Dentistry.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

constituents, including nicotine, noricotine, and anabasine. Nicotine reacts with nitrite to produce specific nitrosamines such as 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone and 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanol. These products lead to the production of reactive oxygen species (ROS), which are known to activate nuclear factor kappa beta (NF- κ B)⁵ and cause DNA mutations that stimulate the growth of oral cancer.⁶

The pathogenesis of oral cancer is not fully understood. Smoking, alcohol consumption, exposure to radiation, and chemical carcinogens are postulated as the main risk factors. Smoking will lead to an inflammatory response in the oral mucosa due to the production of heat, smoke, and the products contained within the cigarettes. These products cause inflammatory responses in the oral mucosa⁷ and can lead to the development of oral cancer.⁸ The inflammation process involves the recruitment of inflammatory cells. One inflammatory cell, which has an important role in the development of oral cancer, is macrophages as this type of cell produces pro-inflammatory cytokine.⁹ Cytokines are essential constituents in the microenvironment of cancers due to their ability to invade and metastasize, and can promote cell proliferation and survival.¹⁰ Other inflammatory cells such as lymphocyte cells are indicators of the onset of chronic inflammation.¹¹

Matrix metalloproteinase 9 (MMP-9) is a protease enzyme that has the potential to be a cancer marker, including oral cancer. MMP-9 is involved in the early development and growth of cancer.¹² Moreover, MMP-9 is an endopeptidase enzyme that has a role in the division and destruction of extracellular matrix substrates, and regulates various protein activities.¹³ It also has a high presence in the gelatinolytic process, which degrades collagen types IV, V, VII, IX, and X, fibronectin, e-cadherin, and elastin. MMP-9 is secreted by cells of the human body, such as fibroblast cells, endothelial cells, polymorphonuclear cells, keratinocytes, macrophages, and epithelial cells.¹⁴ MMP-9 expression increases during cancer growth and therefore considered capable of being a marker for cancer diagnostic and prognosis.¹⁵ However, no studies have evaluated the increase of inflammatory cell and MMP-9 expression during exposure to cigarette smoke. The purpose of this study is to determine the number of macrophages, lymphocytes, plasma cells, and MMP-9 expression on the tongue epithelial of *Rattus norvegicus* exposed to cigarette smoke as an indicator of the risk factor for oral cancer.

Materials and Methods

Animals

All experimental animals were treated by following the regulations on Animal Care and Use Committee of Airlangga University. The protocol was approved by the Health Research Ethical Clearance Committee, Faculty of Dental Medicine with the registration number 181/HRECC.FODM/IX/2017. This study used a sample of 30 *R. norvegicus*—3-month-old male and weighing between 170 and 200 g—that is selected based on the benchmarks of healthy mice, which includes

clear-eyed features, shiny fur, agile movements, and good feces.

Cigarette Smoke Exposure

Cigarette smoke exposure was artificially created using a smoking pump. The animal placed in a room that was connected to a smoking chamber by a valve. The valve serves to equalize the dose of smoke coming into each of the mouse tubes so that the animals were actively exposed to cigarette smoke. Two cigarettes per day were burned and exposed to the animal for either 4 or 8 weeks.

Tissue Collection

After all the animals had been exposed to cigarette smoke for 4 or 8 weeks, excluding the control group who were not exposed, the animals were then sacrificed. The tongues were dissected, and a histology preparation procedure and paraffin block were conducted.

Number of Macrophages, Lymphocytes, and Plasma Cell

The tongue tissue was stained using hematoxylin-eosin to directly count the number of macrophages, lymphocytes, and plasma cell. This was done in five different field light microscopes, with $\times 1,000$ magnification using a Nikon H600L microscope with a 300-megapixel DS Fi2 camera and the Nikon Image System picture software procession.

Matrix Metalloproteinase 9 Expression

The MMP-9 expression is a collagenase type IV proteolytic enzyme in which the observed expression stains a brownish color in the cytoplasm of cells undergoing dysplasia using MMP-9 monoclonal antibodies by immunohistochemical methods. The stain was analyzed by directly counting the immunoreactive cell in the basal and suprabasal regions in 20 different field light microscopes, with $\times 1,000$ magnification using a Nikon H600L microscope with a 300-megapixel DS Fi2 camera and the Nikon Image System picture software procession.

Statistical Analysis

The results of the data obtained were statistically analyzed using the Statistical Package for the Social Sciences. Data analysis was performed by using the Kolmogorov-Smirnov test to test for normality and Levene's test for homogeneity. One-way analysis of variance would be carried out to compare the MMP-9 expression between each treatment group. The number of macrophages, lymphocytes, and plasma cells was analyzed using the Kruskal-Wallis and Mann-Whitney test to compare each treatment group. A *p*-value < 0.05 was considered as different.

Results

Number of Macrophages, Lymphocytes, and Plasma Cell

The number of macrophages, lymphocytes, and plasma cells is presented in **Fig. 1**. The macrophages cells in the tongue

epithelial after 8 weeks of cigarette smoke exposure (10.20 ± 8.69) was greater than 4 weeks of cigarette smoke exposure (8.60 ± 5.29) and the control (5.80 ± 6.29) ($p = 0.000$). The macrophages cells in the tongue epithelial exposed to 4 weeks of cigarette smoke (8.60 ± 5.29) showed a higher number than that of the control group (5.80 ± 6.29 ; $p = 0.014$; **Table 1**).

The lymphocytes cells in the tongue epithelial after 8 weeks of cigarette smoke exposure (23.40 ± 13.26) showed a higher number in comparison to 4 weeks of cigarette smoke exposure (9.80 ± 10.15) and the control group (0.80 ± 2.62 ; $p = 0.000$). The macrophages cells in the tongue epithelial after 4 weeks of cigarette smoke exposure (9.80 ± 10.15) was higher than the control group (4.80 ± 2.62 ; $p = 0.009$; **Table 1**). The plasma cell in the tongue epithelial showed no difference in either 8 or 4 weeks of cigarette smoke exposure when compared to the control group ($p = 0.135$; **Table 1**).

Matrix Metalloproteinase 9 Expression

The MMP-9 expression was calculated from the cytoplasm of the basal and parabasal epithelial cells, which showed brown

MMP-9 expression (**Fig. 2**). The MMP-9 expression in the tongue epithelial after 8 weeks of cigarette smoke exposure (13.10 ± 2.38) showed a higher number than both the 4 weeks of cigarette smoke exposure (8.80 ± 3.46) and the control group (5.00 ± 1.89 ; $p = 0.010$ and $p = 0.000$, respectively). The MMP-9 expression in the tongue epithelial after 4 weeks of cigarette smoke exposure (8.80 ± 3.46) showed a higher number than the control group (5.00 ± 1.89 ; $p = 0.000$; **Table 1**).

Discussion

Continuous exposure to cigarette smoke can cause persistent lesions on the oral mucosa. With such injuries, the body will respond with self-defense, which causes a chronic inflammatory process as a response to long-term cigarette smoke exposure. The occurring inflammation is indicated by the presence of activated inflammatory cells. The chronic inflammation is characterized by the infiltration of mononuclear cells such as macrophages, lymphocytes, and plasma cells in the tissue, resulting in tissue destruction. These cells cause the increase

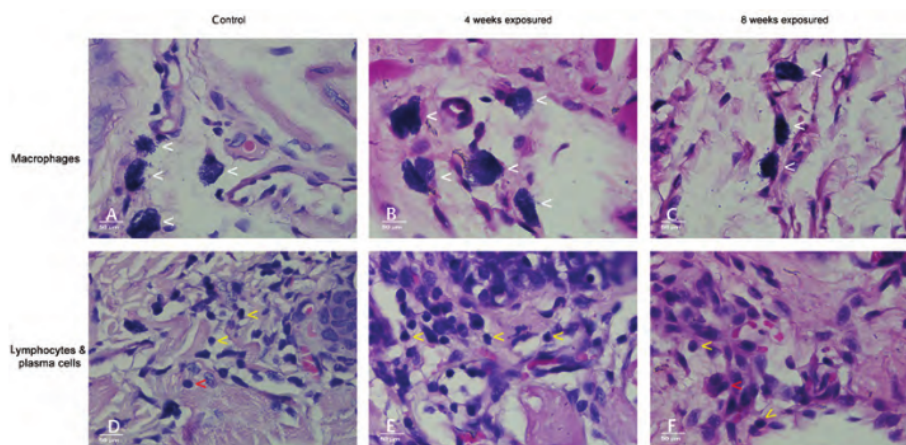


Fig. 1 The macrophages cells (white arrow), lymphocytes (yellow arrow), and plasma cells (red arrow) in the tongue epithelial ($\times 1,000$ magnification). Control group (A, D), 4-week cigarette smoke exposure (B, E), and 8-week cigarette smoke exposure (C, F).

Table 1 The mean of Matrix metalloproteinase 9 expression, number of lymphocytes, macrophages, and plasma cell in the tongue epithelial

Marker	Control	4-week exposure	8-week exposure	p-Value
MMP-9	5.00 ± 1.89^{ab}	8.80 ± 3.46^{ac}	13.10 ± 2.38^{bc}	$0.000^{a,b}$ 0.010^c
Macrophages	5.80 ± 6.29^{de}	8.60 ± 5.29^{df}	10.20 ± 8.69^{ef}	0.014^d $0.000^{e,f}$
Lymphocytes	4.80 ± 2.62^{de}	9.80 ± 10.15^{df}	23.40 ± 13.26^{ef}	0.009^d $0.000^{e,f}$
Plasma cells	0.2 ± 0.63	0	0.7 ± 1.16	0.135^g

Abbreviations: MMP-9, matrix metalloproteinase 9; LST, least significant difference.

Note: the data presented as mean \pm standard deviation. The same character in the marker column shows significant differences in each group.

^{a-c}Significant differences with LSD test, with $p < 0.05$.

^{d-f}Significant differences with the Mann-Whitney test, with $p < 0.05$.

^gSignificant value with Kruskal-Wallis test $p < 0.05$.

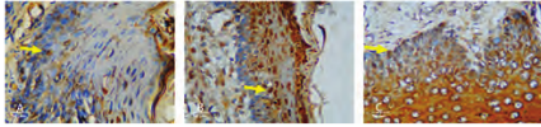


Fig. 2 Matrix metalloproteinase 9 expression around cells and in cytoplasm (yellow arrow; $\times 1,000$ magnification). Control group (A), 4-week cigarette smoke exposure (B), and 8-week cigarette smoke exposure (C).

of ROS.¹⁶ The increase in ROS will cause oxidative stress, which can induce DNA damage and genomic instability.

Lymphocyte cells are seen indicating the onset of chronic inflammation. This inflammation causes widespread cell and tissue damage, causing increased macrophage cell activation. The presence of increased macrophage cells will activate lymphocytes, which are markers of a chronic inflammatory phase. Phagocytosis by these macrophages causes the macrophages to present an antigen that is recognized by T-CD4 lymphocytes. The activation of T-CD4⁺ cells causes an even greater immune response. T-CD4⁺ cells have great potential to produce interleukin 2 (IL-2), which is an interleukin that is very influential in increasing cell proliferation. The IL-2 is not only utilized by T-CD4⁺ cells but also by T-CD8⁺ and B cells, which differentiate into plasma cells.¹¹ Additionally, this research confirmed the increase of lymphocytes and macrophages after exposure to cigarette smoke for 8 weeks. Another study conducted by Zaquia et al supports the results of this study—noting an increase in the inflammatory cell when studying the effect of passive smoking on the larynx and trachea over a period of 120 days—used cigarettes containing 10 mg tar and 0.8 mg nicotine and one cigarette per day for each animal.¹⁷ While this study used cigarettes contained 34 mg tar and 2.1 mg nicotine, the highest content of tar and nicotine not only caused the chronic inflammatory response with the presence of lymphocytes and macrophages but also saw the occurrence of hyperplasia and dysplasia. A previous study by Ayuningtyas et al, which examined cigarette smoke exposure over the course of 4 and 8 weeks with the same cigarette, saw that there were no clinical changes of the oral mucosal specifically on the tongue and oropharyngeal mucosal, but there were histological changes of hyperplasia and dysplasia. At 4 weeks, mild dysplasia developed, and at 8 weeks it changed to moderate and severe dysplasia.^{18,19} The results of the study proved that long-term cigarette smoke exposure and cigarette composition contributed to the risk factor of oral cancer development, along with the presence of hyperplasia and dysplasia as a marker of histological changes; thus, in this study we would like to elucidate cellular and molecular changes due to long-term cigarette smoke exposure through examining level of chronic inflammatory cells infiltration as a marker of chronic inflammation and MMP-9 as a marker for invasion and metastasis.²⁰

No changes can be seen on plasma cell level in this study between control and treatment group was in line to several

previous studies might due to downregulation of B cell. Studies on humans generated contradictory data showing that cigarette smoking increases frequency of memory B cells and IgE production, lowers regulatory B cell numbers, but decreases production of IgA, IgG, and IgM in smokers while smoke exposure downregulates murine marrow pre-B cells or pro-B cells.²¹ Another study showed a number of B cells were not affected by smoking.²² In summary, smoking might alter immune response by affecting B cell.

The results of this study showed an increase in MMP-9 expression proportional to the increased inflammatory cells, which was later confirmed by Ayuningtyas et al, who noted an increase in severity of the degree of dysplasia. The mechanism proves that continuous smoke exposure will cause a chronic inflammatory response accompanied by tissue destruction. Chronic inflammation means a persistent inflammation that causes increased chronic inflammatory cells such as macrophages, lymphocytes, and plasma cells due to increased ROS as a result of exposure to smoke. These chronic inflammatory cells then release the metalloproteinase-9 matrix, which facilitates the occurrence of malignancy.²³ Matrix metalloproteinase is a group of enzymes that can damage the bonds between cells and extracellular matrix. It is thought to play a role in the process of carcinogenesis of epithelial cells, including the oral epithelium. Among many matrixine families, MMP-9 is matrixine type that has the highest collagen degradation activity. Therefore, MMP-9 is more widely observed and considered as a biomarker for the diagnosis and prognosis of cancer. MMP-9 is secreted by fibroblast cells, endothelial cells, and inflammatory cells such as polymorphonuclear neutrophils, keratinocytes, and macrophages. Moreover, MMP-9 plays a role in carcinogenesis in two stages. The first stage is actively involved in the occurrence of dysplasia and is followed by the next stage in the development of dysplasia toward carcinoma.²³ In the early stages, MMP-9 plays a role in cell proliferation by activating several growth factors, such as a transformative growth factor α (TGF- α) which might induce hyperplasia, as well as damaging the attachment between cells to form microenvironment, which supports changes in cell morphology lead to metastasis. The inflammatory mediators, including NF- κ B, vascular endothelial growth factor, inflammatory cytokines, prostaglandin pathways, p53 activation,^{24,25} reactive oxygen and nitrogen species, and microRNAs, are major players in the pathogenesis of oral cancer.⁵ Activation of ROS has a pathological effect besides causing DNA mutations, such irritating the mucous membrane, which causes an inflammatory reaction. Moreover, ROS also degrades inhibitory kappa B (I κ B), which causes an increase in NF- κ B in the nucleus. This attracts more inflammatory cells such as neutrophils and macrophages. These inflammatory cells produce MMP-9 collagenase enzymes that have destructive abilities, E-cadherin, which is the adhesive between cells. MMP-9 also damages collagen type 4, damaging fibronectin and elastin, which facilitates dysplasia.²⁶ Similarly, ROS also causes a decrease in the tissue inhibitor of metalloproteinase (TIMP-1) expression by transforming the growth factor $\beta 1$ (TGF- $\beta 1$), which is an antiproliferative agent. TIMP-1 is a

natural inhibitor of MMP-9; thus, the inhibition of TIMP-1 production causes the excessive expression of MMP-9.¹⁵

The results also show the presence of MMP-9 expression in normal epithelial tissue. The MMP-9 expression was present in the cytoplasm and cell-extracellular tissue due to the activity of fibroblasts which can induce MMP-9 expression in physiological processes.^{27,28} The MMP-9 expression in the noncigarette smoke exposed group was lower than the groups of 4 and 8 weeks cigarette smoke exposure. The increase of MMP-9 expression was followed by an increase in the inflammatory cells.

Conclusion

Cigarette smoke exposure induces the risk of oral cancer development due to the increased number of macrophages, lymphocytes and MMP-9 expressions in the tongue epithelial.

Funding

This study is funded by the Faculty of Dental Medicine Universitas Airlangga 2019 in the Schema Penelitian Unggulan Fakultas.

Conflict of Interest

None declared.

References

- 1 Idris S, Baqays A, Isaac A, Chau JKM, Calhoun KH, Seikaly H. The effect of second hand smoke in patients with squamous cell carcinoma of the head and neck. *J Otolaryngol Head Neck Surg* 2019;48(1):33
- 2 Sierra H, Cordova M, Chen CJ, Rajadhyaksha M. Confocal imaging-guided laser ablation of basal cell carcinomas: an ex vivo study. *J Invest Dermatol* 2015;135(2):612–615
- 3 Ghallab NA, Shaker OG. Serum and salivary levels of chemerin and MMP-9 in oral squamous cell carcinoma and oral premalignant lesions. *Clin Oral Investig* 2017;21(3):937–947
- 4 Sood P, Narang R, Swathi V, Mittal L, Jha K, Gupta A. Dental patient's knowledge and perceptions about the effects of smoking and role of dentists in smoking cessation activities. *Eur J Dent* 2014;8(2):216–223
- 5 Patel JB, Shah FD, Joshi GM, Patel PS. Clinical significance of inflammatory mediators in the pathogenesis of oral cancer. *J Cancer Res Ther* 2016;12(2):447–457
- 6 Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. *Int J Environ Res Public Health* 2009;6(2):445–462
- 7 Sundar IK, Javed F, Romanos GE, Rahman I. E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. *Oncotarget* 2016;7(47):77196–77204
- 8 Tampa M, Mitran MI, Mitran CI, et al. Mediators of inflammation: a potential source of biomarkers in oral squamous cell carcinoma. *J Immunol Res* 2018;2018:1061780
- 9 Ng WK, Wong SH, Ng SC. Changing epidemiological trends of inflammatory bowel disease in Asia. *Intest Res* 2016;14(2):111–119
- 10 Goertzen C, Mahdi H, Laliberte C, et al. Oral inflammation promotes oral squamous cell carcinoma invasion. *Oncotarget* 2018;9(49):29047–29063
- 11 Bhat TA, Kalathil SG, Bogner PN, et al. Secondhand smoke induces inflammation and impairs immunity to respiratory infections. *J Immunol* 2018;200(8):2927–2940
- 12 Gracia I, Utoro T, Supriatno S, Astuti I, Heriyanto DS, Pramono D. Epidemiologic profile of oral squamous cell carcinoma in Yogyakarta, Indonesia. *Padjadjaran J Dent* 2017;29(1):32–37
- 13 Venugopal A, Uma Maheswari TN. Expression of matrix metalloproteinase-9 in oral potentially malignant disorders: a systematic review. *J Oral Maxillofac Pathol* 2016;20(3):474–479
- 14 Peschos D, Damala C, Stefanou D, et al. Expression of matrix metalloproteinase-9 (gelatinase B) in benign, premalignant and malignant laryngeal lesions. *Histol Histopathol* 2006;21(6):603–608
- 15 Chandolia B, Basu SK, Kumar M. Can MMP-9 be a prognosticator marker for oral squamous cell carcinoma? *J Clin Diagn Res* 2016;10(1):ZC09–ZC13
- 16 Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation: cellular and molecular mechanisms. *J Dent Res* 2012;91(2):142–149
- 17 Zaquia Leão H, Galleano Zettler C, Cambruzzi E, et al. The effects of passive smoking on laryngeal and tracheal mucosa in male wistar rats during growth: an experimental study. *J Voice* 2017;31(1):126.e19–126.e24
- 18 Ayuningtyas NF, Mahardika GO, Soebadi B, et al. Hyperplasia of Wistar rat tongue mucosa due to exposure to cigarette side-stream smoke. *Dent J* 2019;52(3):133
- 19 Ayuningtyas NF, Endah A, Permatasari A, et al. The increase of dysplasia level in Wistar rats oropharyngeal mucosa exposed by sidestream cigarette smoke. *Eurasia J Biosc* 2020;14:3641–3646
- 20 de Oliveira Semenzati G, de Souza Salgado B, Rocha NS, Michelin Matheus SM, de Carvalho LR, Garcia Martins RH. Histological and immunohistochemical study of the expression of p53 and ki-67 proteins in the mucosa of the tongue, pharynx and larynx of rats exposed to cigarette smoke. *Inhal Toxicol* 2012;24(11):723–731
- 21 Qiu F, Liang C-L, Liu H, et al. Impacts of cigarette smoking on immune responsiveness: up and down or upside down? *Oncotarget* 2017;8(1):268–284
- 22 Loos BG, Roos MTL, Schellekens PTA, van der Velden U, Miedema F. Lymphocyte numbers and function in relation to periodontitis and smoking. *J Periodontol* 2004;75(4):557–564
- 23 Hauff SJ, Raju SC, Orosco RK, et al. Matrix-metalloproteinases in head and neck carcinoma-cancer genome atlas analysis and fluorescence imaging in mice. *Otolaryngol Head Neck Surg [Internet]* 2014;151(4):612–618
- 24 Irmawati A, Handayani ATW, Balqis NF, Surboyo MDC. The decreased of p53 mutant expression on squamous cell epithelial of oral in mus musculus by moderate intensity of exercise. *Malaysian J Med Heal Sci* 2020;16(July):1–5
- 25 Arundina I, Budhy TI, Surboyo MDC. Meloxicam inhibit the growth of oral squamous cell carcinoma induced by benzopyrenes. *Malaysian J Med Heal Sci* 2020;16(4):22–25
- 26 Fan HX, Li HX, Chen D, Gao ZX, Zheng JH. Changes in the expression of MMP2, MMP9, and ColIV in stromal cells in oral squamous tongue cell carcinoma: relationships and prognostic implications. *J Exp Clin Cancer Res* 2012;31(1):90
- 27 Tsai CH, Hsieh YS, Yang SF, Chou MY, Chang YC. Matrix metalloproteinase 2 and matrix metalloproteinase 9 expression in human oral squamous cell carcinoma and the effect of protein kinase C inhibitors: preliminary observations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod [Internet]* 2003;95(6):710–716
- 28 Murnane MJ, Cai J, Shuja S, McAneny D, Willett JB. Active matrix metalloproteinase-2 activity discriminates colonic mucosa, adenomas with and without high-grade dysplasia, and cancers. *Hum Pathol* 2011;42(5):688–701

The Response of the Tongue Epithelial on Cigarette Smoke Exposure as a Risk Factor for Oral Cancer Development

ORIGINALITY REPORT

20%

SIMILARITY INDEX

12%

INTERNET SOURCES

19%

PUBLICATIONS

1%

STUDENT PAPERS

PRIMARY SOURCES

1	www.oncotarget.com Internet Source	1%
2	www.dovepress.com Internet Source	1%
3	OZYILDIZ, Zafer, YILMAZ, Rahsan, OZSOY, Sule Yurdagul and OZKUL, I. Ayhan. "Parasitic aortitis due to onchocerca armillata in slaughtered cattle in the southeastern region of Turkey", Kafkas Üniversitesi, 2013. Publication	1%
4	hal.sorbonne-universite.fr Internet Source	1%
5	www.scientificarchives.com Internet Source	1%
6	Meircurius Dwi Condro Surboyo, Ira Arundina, Retno Pudji Rahayu, Dieni Mansur, Taufan Bramantoro. "Potential of Distilled Liquid Smoke Derived from Coconut (Cocos nucifera	1%

L) Shell for Traumatic Ulcer Healing in Diabetic Rats", European Journal of Dentistry, 2019

Publication

7

Retno Indrawati Roestamadji, Nahdah Izdihar Nastiti, Meircurius Dwi Condro Surboyo, Anis Irmawati. "The Risk of Night Shift Workers to the Glucose Blood Levels, Saliva, and Dental Caries", European Journal of Dentistry, 2019

Publication

1 %

8

Andrew Strasser, Viba Malaiyandi, Ewa Hoffmann, Rachel Tyndale, Caryn Lerman. "An association of CYP2A6 genotype and smoking topography", Nicotine & Tobacco Research, 2007

Publication

1 %

9

Elly Munadziroh, Muhammad Genadi Askandar, Anita Yuliati, Meircurius Dwi Condro Surboyo, Wan Himratul Aznita Wan Harun. "The effect of secretory leukocyte protease inhibitor amnion membrane on incisional wound healing", Journal of Oral Biology and Craniofacial Research, 2022

Publication

1 %

10

Intan Nirwana, Elly Munadziroh, Anita Yuliati, Azalia Izzah Fadhila et al. "Ellagic acid and hydroxyapatite promote angiogenesis marker in bone defect", Journal of Oral Biology and Craniofacial Research, 2022

Publication

1 %

11	ejobios.org Internet Source	1 %
12	G. Poli. "Tubal ectopic pregnancy: macrophages under the microscope", Human Reproduction, 07/25/2007 Publication	1 %
13	Marlena Matulka, Aneta Konopka, Barbara Mroczko, Anna Pryczynicz et al. "Expression and Concentration of Matrix Metalloproteinase 9 and Tissue Inhibitor of Matrix Metalloproteinases 1 in Laryngeal Squamous Cell Carcinoma", Disease Markers, 2019 Publication	1 %
14	link.springer.com Internet Source	<1 %
15	en.wikipedia.org Internet Source	<1 %
16	www.febrasgo.org.br Internet Source	<1 %
17	Ardite, E.. "Systemic effects of cigarette smoke exposure in the guinea pig", Respiratory Medicine, 200607 Publication	<1 %
18	Jingqiu Bu, Xi Bu, Bing Liu, Fei Chen, Peng Chen. "Inhibition of metastasis of oral	<1 %

squamous cell carcinoma by anti-PLGF treatment", Tumor Biology, 2014

Publication

19

Qingqing Zhou, Rui Jia, Jingxia Dang. "Correlation between the Neutrophil-to-Lymphocyte Ratio and Multiple Sclerosis: Recent Understanding and Potential Application Perspectives", Neurology Research International, 2022

Publication

20

Yafang Li, Zhichuang Lian, Qifeng Li, Wei Ding, Wenyi Wang, Ling Zhang, Xirennayi Muhataer, Yuan Zhou, Xiaohong Yang, Chao Wu. "Molecular mechanism by which the Notch signaling pathway regulates autophagy in a rat model of pulmonary fibrosis in pigeon breeder's lung", Open Medicine, 2023

Publication

21

lipidworld.biomedcentral.com

Internet Source

22

www.physiology.org

Internet Source

23

"1-A1: Lung Cancer 1 : Poster Sessions", Respirology, 2013.

Publication

24

Benedette J. Cuffari, Hemanta C Rao Tumu, Maria A. Pino, Blase Billack. "Assessment of

<1 %

<1 %

<1 %

<1 %

<1 %

<1 %

the time-dependent dermatotoxicity of mechlorethamine using the mouse ear vesicant model", *Interdisciplinary Toxicology*, 2018

Publication

25

Chenglin Luo, Jingjing Cao, Rui Peng, Qiaoyun Guo, Hua Ye, Peng Wang, Kaijuan Wang, Chunhua Song. "Functional Variants in Linc-ROR are Associated with mRNA Expression of Linc-ROR and Breast Cancer Susceptibility", *Scientific Reports*, 2018

<1 %

Publication

26

Erdem, N.F.. "Characterization of 3 Oral Squamous Cell Carcinoma Cell Lines With Different Invasion and/or Metastatic Potentials", *Journal of Oral and Maxillofacial Surgery*, 200709

<1 %

Publication

27

I-Neng Lee, Martin Hsiu-Chu Lin, Chiu-Yen Chung, Ming-Hsueh Lee, Hsu-Huei Weng, Jen-Tsung Yang. "Chronic cigarette smoke exposure enhances brain-derived neurotrophic factor expression in rats with traumatic brain injury", *Metabolic Brain Disease*, 2012

<1 %

Publication

28

Saskia Braber, Paul AJ Henricks, Frans P Nijkamp, Aletta D Kraneveld, Gert Folkerts.

<1 %

"Inflammatory changes in the airways of mice caused by cigarette smoke exposure are only partially reversed after smoking cessation",
Respiratory Research, 2010

Publication

29

Sven E. Niklander. "Inflammatory Mediators in Oral Cancer: Pathogenic Mechanisms and Diagnostic Potential", Frontiers in Oral Health, 2021

Publication

30

Wei-Yin Zheng, Ding-Tao Zhang, Shu-Yong Yang, Hao Li. "Elevated Matrix Metalloproteinase-9 Expression Correlates With Advanced Stages of Oral Cancer and Is Linked to Poor Clinical Outcomes", Journal of Oral and Maxillofacial Surgery, 2015

Publication

31

bmccancer.biomedcentral.com
Internet Source

<1 %

32

deepblue.lib.umich.edu
Internet Source

<1 %

33

jcd.org.in
Internet Source

<1 %

34

uod.ac
Internet Source

<1 %

35

www.podj.com.pk
Internet Source

<1 %

36

"Lasers in Dermatology and Medicine",
Springer Science and Business Media LLC,
2018

Publication

<1 %

37

A. M. Tuttle. "Cigarette smoke causes follicle
loss in mice ovaries at concentrations
representative of human exposure", Human
Reproduction, 02/19/2009

Publication

<1 %

38

A. Uruchurtu Marroquin, M. Ajmal.
"Carrageenin-induced arthritis in the specific-
pathogen-free pig", Journal of Comparative
Pathology, 1970

Publication

<1 %

39

Encep Abdurahman, Nengdiana Permana,
Grace Selly Mardiana, Afifah Bambang
Sutjiatmo et al. "Administration of Water
Extract of Stachytarpheta Jamaicensis L. Vahl
Affects Haematological Profile on Animal
Induced Imiquimod", IOP Conference Series:
Earth and Environmental Science, 2022

Publication

<1 %

40

Haodi Dong, Hongxiu Diao, Ying Zhao, Huihao
Xu et al. "Overexpression of matrix
metalloproteinase - 9 in breast cancer cell
lines remarkably increases the cell malignancy
largely via activation of transforming growth

<1 %

factor beta/SMAD signalling", Cell Proliferation, 2019

Publication

41

Herszényi, László, István Hritz, Gábor Lakatos, Mária Varga, and Zsolt Tulassay. "The Behavior of Matrix Metalloproteinases and Their Inhibitors in Colorectal Cancer", International Journal of Molecular Sciences, 2012.

Publication

<1 %

42

Leah R. Miller. "Cigarette smoke and dopaminergic system", Journal of Biochemical and Molecular Toxicology, 11/2007

Publication

<1 %

43

Mari S Golub, Carl L Keen. "Effects of Dietary Aluminum on Pubertal Mice", Neurotoxicology and Teratology, 1999

Publication

<1 %

44

Samah Mohamed Elhomosy, Fatma Mohamed Abdallah Elshobary, Ashour E.S.. "Effectiveness of Nursing Intervention on Sexual Health of Women Undergoing Direct-Acting Antiviral Drugs for Hepatitis C Virus", Egyptian Journal of Health Care, 2022

Publication

<1 %

45

Thao Phuong Bui, Anh Ngoc Hoang, Phuong Lan Le, Bich Thi Pham, Linh Thi Tu Nguyen, Ha Minh Do, To Van Ta, Thai Hong Trinh. "Matrix

<1 %

metalloproteinases in Vietnamese patients with colorectal cancer", Oncology Letters, 2017

Publication

46

ash.org

Internet Source

<1 %

47

e-journal.unair.ac.id

Internet Source

<1 %

48

innovareacademics.in

Internet Source

<1 %

49

pure.amc.nl

Internet Source

<1 %

50

www.jidmr.com

Internet Source

<1 %

51

"Oral Cancer Detection", Springer Science and Business Media LLC, 2019

Publication

<1 %

52

Claire Lager, Riley Perry, Jonathan Daly, Christopher Page et al. "Metrics of Coral Microfragment Viability", Cold Spring Harbor Laboratory, 2023

Publication

<1 %

53

Min-Hsiung Pan, Ching-Shu Lai, Hong Wang, Chih-Yu Lo, Chi-Tang Ho, Shiming Li. "Black tea in chemo-prevention of cancer and other

<1 %

human diseases", Food Science and Human Wellness, 2013

Publication

54

Stanley M. H. Chan, Kurt Brassington, Suleman Abdullah Almerdasi, Aleksandar Dobric et al. "Inhibition of oxidative stress by apocynin attenuated chronic obstructive pulmonary disease progression and vascular injury by cigarette smoke exposure", British Journal of Pharmacology, 2023

Publication

<1 %

Exclude quotes Off

Exclude matches Off

Exclude bibliography On

The Response of the Tongue Epithelial on Cigarette Smoke Exposure as a Risk Factor for Oral Cancer Development

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5
