Association of Tooth Loss and Risk of Lung Cancer in a Greek Adult Population: A Case-Control Study

Nikolaos Andreas Chrysanthakopoulos[1*]

[1]DDSc, Oncologist (MSc Oncol), PhD in Oncology (cand), Athens, Greece

*Corresponding Author: Nikolaos Andreas Chrysanthakopoulos, DDSc, Oncologist (MSc Oncol), PhD in Oncology (cand), Athens, Greece

Abstract

To evaluate the potential connection among the numeral of missing teeth and the risk of LC in three private treatments of outpatients in Greece.

Keywords: Periodontitis; Lung Carcinoma; Cancer risk; Tooth loss; Adults; Chronic inflammation.

Introduction

Lung cancer (LC) is currently the fifth leading cause of death in developed countries [2,3]. The majority of LC cases are genetic factors such as male gender, age, enzyme polymorphism, family history and geneticpredisposition, smoking, behavioral and environmental factors such as inhalation of contaminated air/industrial gas/radon particles and may be due to bad eating habits [2,3].

Chronic inflammation leads to activation of cellular signaling pathways involved in mutagenesis, increased cell proliferation and release of inflammatory biomarkers and other signaling mediators, limited adaptation to oxidative stress, and reactive production.

The possible association between both diseases could be attributed to various reasons as having certain risk factors in common, have as advanced age,cigarette smoking, and low socio-economic status (SES) [43]. One of the biggest challenges in studying periodontitis using observational studies concerns the measurement of PD. Thus, tooth loss can represent several oral conditions, is often only a crude marker of periodontitis, and may vary dramatically depending onthe population, asit has beenshownthatinhealth professionals more than half (58%) hado-16 remaining teeth but did not suffer from periodontitis [23]. Tooth loss is also an SES marker. Missing teeth isattributedto dentalcariesandPD, however, the parameter of age is crucial forthe distribution of all causes, as at an older age the main cause is chronic PD whereasat younger ages themain causeisdentalcaries [6].

Materials and Methods

Study design

The current report was based on a case-control design and was performed between December 2019 and December 2020. This procedure resulted in a study sample of 605 individuals. Participants enrolled in the study protocol after their selection from three private practices, two medical and one dental, completed a self-administered questionnaire regarding their medical and dental history and their dental clinical examination was carried out by a well-trained and calibrated Dental Surgeon.

Cases and Controls selection criteria

The participants should not have received, during the previous six months, any type of conservative or surgical periodontal treatment, and should not have received any treatment.

Similarly excluded those who received medication or general glucocorticoids for the mentioned pathological conditions. Patients with an advanced stage of LC under treatment such as chemotherapy or radiotherapy, those with metastatic LC, mesothelioma, and patients with aprimary focuson the head-neck-thorax region (carcinogenesis field theory) [47].

The case group consisted of LC patients in whom the diagnosis was based on histological examination after performing their endoscopic procedure.

Medical and Dental Questionnaire

I filled out the Medical Questionnaire [48] at Minnesota Dental School. Subjects were categorized into 4549, 5059, 6069 and 70+by age.

Education level such as elementary school, university/university degree. If the SES is less than 1,000 and more than €1,000/month. Smoking status as a person who has never smoked and as a former/current smoker. Presence or absence of family history of LC and presence of previous lung disease (COPD, TB, ILF).

Clinicalexamination

Using the standard 28 teeth as a reference, assessing the number of existing teeth and subtracting the number of 28 existing teeth will result in the loss or loss of some teeth. Defined as a tooth.

The clinical assessment of PPD was about immediate complete millimeters. 125 (20%) individuals, cases, and controls, randomly selected, were reexamined for determining the intraexaminer variance, by the same Dental Surgeon and no difference.

Statistical analysis

Mean PPD at 6 sites per subject's teeth was measured and encoded as a dichotomous variable. Male participants, participants with higher educational status (university level) and socioeconomic status (income/monthly>€1,000),active/exsmokers, family history of LC or previous chronic lung disease People, and individuals suffering from LC cases, were also coded as 1 and individuals with moderate and severe periodontal pockets were also coded as 1.

Results

The mean age of the participants, cases and controls, was 64,4 years (± 3.2). Squamous cell carcinoma(SCC) (43.6%), small cell carcinoma(SCLC) (35.4%),

adenocarcinoma(AC) (11.2%)and largecellcarcinoma (LCC)(9.8%), wasthedistribution of LC histological types in males, whereas in females the corresponding distribution was AC (47.8%), SCC(36.3%), SCLC (9.7%) and LCC (6.2%).

Table1presents the epidemiological variables according to the univariate analysis and shows that smoking (p=0.000) and previous chronic lung disease (p=0.014), were statistically significantly associated with risk for LC development, whereas PPD (p=0.076)and missing teeth (p=0.065) were not. UOR's and 95% CI shown in table 1.

Table 1: Univariate analysis of cases and controls regarding each independent variable examined.

Gender	Cases	Controls	P-value	Odds Ratio and 95%Confidence Interval
Males	90 (58.1)	229 (50.9)	0.123	0.748 (0.518-1.082)
Females	65 (41.9)	221 (49.1)		
Age 45-49	12 (7.7)	31 (29.3)		
50-59	29 (18.7)	99 (47.3)	0.783	_____
60-69	91 (58.7)	248 (23.4)		
70+	23 (14.8)	72 (16.0)		
Educational level Low	119 (76.8)	328 (72.9)	0.342	1.230 (0.802-1.884)
High	36 (23.2)	122 (27.1)		
S/economic level Low	91 (58.7)	275 (61.1)	0.598	0.905 (0.624-1.312)
High	64 (41.3)	175 (38.9)		
Smoking status No	42 (27.1)	220 (48.9)	**0.000***	0.389 (0.261-0.579)
Yes	113 (72.9)	230 (51.1)		
Cancer family history No	105 (67.7)	297 (66.0)	0.692	1.082 (0.733-1.597)
Yes	50 (32.3)	153 (34.0)		
Previous lung disease No	87 (56.1)	302 (67.1)	**0.014***	0.627 (0.432-0.911)
Yes	68 (43.9)	148 (32.9)		
Depth of Probing pocket 0-3.00 mm	103 (68.7)	342 (76.0)	0.076	0.692 (0.461-1.040)
≥ 4.0 mm	47 (31.3)	108 (24.0)		

Tooth loss						
None	12 (7.7)	42 (9.3)				
1-4	28 (18.1)	93 (20.7)	0.065		_____	
5-10	47 (30.3)	171 (38.0)				
>10	68 (43.9)	144 (32.0)				

By applying a multivariate regression analysis model (Enter and Wald methods), smoking (p=0.000), deep periodontal pockets (p=0.048), and the number of missing teeth greater than 4 are statistically at risk of developing LC. It was shown to be significantly related Table 2. Table 2 also shows AOR and 95% CI.

Table 2: Presentation of association between potentially risk factors and LC according to Enter (first step-1ᵃ) and Wald (last step 6ᵃ) method of multivariate logistic regression analysis model.

Variables in the Equation								
							95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1ᵃ	gender	,035	,203	,029	1	,364	1,035	,695	1,543
	age	,641	,116	1,735	1	,095	,527	,420	,661
	socioec.level	,038	,221	,045	1	,498	1,000	,649	1,543
	educ.level	,361	,240	2,267	1	,132	,697	,436	1,115
	smok.stat	1,135	,230	8,381	1	,000*	3,110	1,982	4,879
	cancer.fam.hist	,240	,226	1,121	1	,290	,787	,505	1,226
	prev.lung.dis	,244	,218	1,246	1	,264	1,276	,832	1,957
	prob.pock.depth	,603	,240	3,326	1	,052	1,828	1,142	2,925
	tooth.loss (none)			8,143	3	,043*			
	tooth.loss(1-5)	-,462	,391	3,065	1	,044*	1,182	,178	1,322
	tooth.loss(6-10)	,494	,286	3,094	1	,034*	1,610	,549	1,904
	tooth.loss(>10)	,451	,241	3,512	1	,051	1,237	,597	1,921
	Constant	,468	,329	2,029	1	,154	,626		
Step 6ᵃ	smok.stat	1,160	,222	8,276	1	,000*	3,192	2,065	4,933
	prob.pock.depth	,637	,223	3,142	1	,048*	1,890	1,221	2,927
	tooth.loss (none)			8,147	3	,041*			
	tooth.loss(1-4)	-,471	,388	3,263	1	,040*	1,379	,377	1,810
	tooth.loss(5-10)	,401	,277	3,092	1	,032*	1,670	,489	1,953
	tooth.loss(>10)	,465	,236	3,861	1	,047*	1,884	,495	1,209
	Constant	,535	,283	3,583	1	,158	,586		

After controlling for possibleconfounding factors, smoking status and SES, the assessed associations remained significant (Table 3).

Table 3: Smoking status and SES

Tooth loss (Ref: None)	Exp (B)	95% (Confidence Interval) CI
1-4teeth		

Smoking	0.306	0.096-0.976
No smoking	0.764	0.268-2.180
5-10teeth		
Smoking	0.235	0.079-0.702
No smoking	0.612	0.224-1.670
>10teeth		
Smoking	0.267	0.092-0.770
No smoking	0.455	0.178-1.163
1-4teeth		
Low SES	1.167	0.742-1.689
High SES	0.734	0.312-1.103
5-10teeth		
Low SES	1.338	0.807-1.715
High SES	0.802	0.371-1.114
>10teeth		
Low SES	1.523	0.887-1.782
High SES	1.048	0.404-1.206

Discussion

Current case-control studies have shown that smokers with deep periodontal pockets greater than 4.0 mm and lacking four or more teeth are significantly at increased risk of developing LC. Based on these observations, it may be suggested that smoking cessation and improved oral hygiene may reduce the risk of developing LC. However, further investigation is needed to confirm such results [22,23].On the contrary, similar studies have revealed that females [51,52] and males [53,54] Several studies have used large sample sizes, to increase their out comes precision regarding the association between SES and LC, or cancer in general [83,84]. However, these studies have been influenced by the absence of data on important risk factors for LC [84] or have associated aggregate socioeconomic exposure data to individual-level disease status [83,84]. Delegating characteristics of a group to a person may not be proper and may lead to incorrect outcomes, especially if the exposure to that characteristic, as SES, is inaccurately categorized [85, 86]. The current study recorded no association between educational level and LC risk. Previous reports have revealed a higher risk of malignant diseases, especially smoking-related cancers, among the lowest educationallevel individuals andsupported that the higher the level ofeducational attainment, thelower the LCrisk[72,77,87-89]. On the contrary, Faggianoetal. [90]foundthatLC wasmore frequent in higher social strata, whereas the same author in another report observed that the association between educational level (primary school vs. university) andLC risk wasnegative for males (OR = 2.47) and positive for females (OR= 0.62) [91]. A genetic predisposition has been suggested for developing LC[92,93]. It has been found that regardless of smoking status, individuals with an LC family history had increased risk for developing the disease [94-98]. The findings of the current research did not confirm that suggestion. Pre-existing non-malignant lung diseases such as COPD, chronic bronchitis and emphysema [99], TBC and ILF have been associated with an increased risk for developing LC [100]. COPD is an

independentriskfactor for SCC development [101], as those patients showeda 2-5 times higher risk for developingLC, whereasLC occurrenceis uptofive times more probably to have appearedin smokers withairflow obstructionthanthose withnormal lung function [102]. The observationthatCOPDpatientsshowahighpr evalence ofLC can be attributed to commonmechanisms such asprematurelung aging, geneticsusceptibilitytobothdiseases or common pathogenic factors, such asgrowthfactors, intracellular signalingpathways activation or epigenetic influences [103]. Tobacco is a shared risk factor of the mentioned lung diseases and LC. The mechanisms by which those lung diseases may independently influence LC risk remain unknown, but ithasbeensuggestedthat inflammation causedby thosediseasesmay act asa catalyst in the development of lung neoplasms[104]. Moreover, little is known about the association between COPD and the risk of developing LC, particularly in non-smokers, as are rarely affected by the disease. Non-smokers COPD patients exposed to indoor pollutants are at higher risk for developing LC [105]. Zheng et al. [66] recorded that individuals with TBC had a 50% increased risk of LC. A study by Hind et al. [67] regarding LC riskamong smokers andnonsmokerswithTBCshowedthatfemale swith TBC, never-smokers, hadapproximatelyeight times higher risk of LC, whereas no association was foundbetweenfemales smokers. The main limitation of that study was the small number of non-smoking patients with LC [67]. Patients with ILF or other fibrotic diseases had an increased risk of LC, but these potential risk factors have not been accurately identified in nonsmokers [106,107]. No association was recorded in the present report between pre-existing chronic lung disease and risk for LC development. Smoking isa confirmedrisk factor of total cancerand LC [108], as ismainlyinvolved in SCC andSCLC development, andin fewer casesin lungACdevelopment. However, till now the reasons why only 15% of smokers develop LC remain unidentified [109]. The outcomes of the current study confirmed the association examined. Moreover, smoking acts as a confounding factor and is involved in PD development and progression [40]. The outcomes also showed that individuals with deep periodontal pockets were at significantly higher risk for LC. A small number of studies, prospective and based on questionnaires and self-reported data have investigated the possible link between PD indices and LC risk, or total cancer. In a prospective co-twin study [36] was recorded that PD patientshad a higher risk of developing LC, however after adjustment for known confounding factors age, gender, educational level and SES the assessed association was not statistically significant. In another similar study [21] was found that PD patients had an increased risk of total cancer and a significantly increased LC risk, finding that was not confirmed in never smokers. After adjustment for known risk factors for LC, the extent of the association between periodontitis and LC ranged between1.48 and 1.73.

Conclusions

In conclusion, those with deep periodontal pockets and missing four or more teeth

had a significantly higher risk of lung cancer. These associations persisted after controlling certain confounding factors such as smoking status and SES.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30.
2. Causes of death mortality and global health estimates. WHOreport, 2012
3. DavilaDG, WilliamsDE.Theetiologyof lungcancer. Mayo Clin Proc. 1993; 68:170-82.
4. Chrysanthakopoulos NA, Dareioti NS. An Exploration of the Inflammation Cancer Association, Part I. Clin Case Reports Rev. 2018; 4(1): 1-7.
5. Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest. 2003;123(1):21S-49S.
6. Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol. 1996;1(1):1-36.
7. Demmer RT, Desvarieux M. Periodontal infections and cardiovascular disease: the heart of the matter. J Am Dent Assoc. 2006;137:S14-20.
8. Mattila KJ, Pussinen PJ, Paju S. Dental infections and cardiovascular diseases: a review. J Periodontol. 2005;76:2085-8.
9. Joshipura KJ, Wand HC, Merchant AT, Rimm EB. Periodontal disease and biomarkers related to cardiovascular disease. J Dent Res. 2004;83(2):151-5.
10. Loos BG. Systemicmarkersofinflammationinperiodontitis. J Periodontol.2005:2106-15.
11. Amabile N et.al, Severity of periodontal disease correlates to inflammatory systemic status and independently predicts the presence and angiographic extent of stable coronary artery disease. J Intern Med. 2008;263(6):644-52.
12. D'Aiuto F et.al, Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res. 2004;83(2):156-60.
13. Beck JD, Offenbacher S. Systemic effects of periodontitis: epidemiology of periodontal disease and cardiovascular disease. J Periodontol. 2005;76:2089-100.
14. Renvert S, Lindahl C, Roos-Jansåker AM, Lessem J. Short-term effects of an anti-inflammatory treatment on clinical parameters and serum levels of C-reactive protein and proinflammatory cytokines in subjects with periodontitis. J Periodontol. 2009;80(6):892-900.
15. Vidal F, Figueredo CM, Cordovil I, Fischer RG. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension. J Periodontol. 2009;80(5):786-91.
16. Holmstrup P, Poulsen AH, Andersen L, Skuldbøl T, Fiehn NE. Oral infections and systemic diseases. Dent Clin N Am. 2003;47(3):575-98.
17. Correa P. Bacterial infections as a cause of cancer. Journal of the National Cancer Institute. 2003;95(7):E3
18. Shapiro KB, Hotchkiss JH, Roe DA. Quantitative relationship between oral nitrate-reducing activity and the endogenous formation of N-nitrosoamino acids in humans. Food Chem Toxicol. 1991;29(11):751-5.
19. Soory M. Oxidative stress induced mechanisms in the progression of periodontal diseases and cancer: a common approach to redox homeostasis? Cancers. 2010;2(2):670-92.
20. Kostic AD et.al, Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell host & microbe. 2013;14(2):207-15.
21. Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis–cancer association. Ann Epidemiol. 2003;13(5):312-6.
22. Michaud DS, Joshipura K, Giovannucci E, Fuchs CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst. 2007;99(2):171-5.
23. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. The lancet oncology. 2008;9(6):550-8.
24. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. Jama. 2004;291(5):585-90.
25. Heikkilä K et.al, Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. Cancer causes & control. 2009;20(1):15-26.
26. Zheng T et.al, Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. Cancer Causes & Control. 1990;1(3):235-41

27. Garrote LF et.al, Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. Br J Cancer. 2001;85(1):46-54.

28. Rosenquist K. Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Swed Dent J. Supplement. 2005(179):1.

29. Abnet CC et.al, Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes & Control. 2001;12(9):847-54.

30. Abnet CC et.al, Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort. Int J Epidemiol. 2005;34(2):467-74.

31. Abnet CC et.al, Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. Scand J Gastroenterol. 2005;40(6):681-7.

32. Stolzenberg-Solomon RZ et.al, Tooth loss, pancreatic cancer, and Helicobacter pylori. Am J Clin Nutr. 2003;78(1):176-81.

33. Joshipura KJ, Douglass CW, Willett WC. Possible explanations for the tooth loss and cardiovascular disease relationship. J Periodontol. 1998;3(1):175-83.

34. Hiraki A, Matsuo K, Suzuki T, Kawase T, Tajima K. Teeth loss and risk of cancer at 14 common sites in Japanese. Cancer Epidemiol Biomarkers Prev. 2008;17(5):1222-7.

35. Mai X et.al, History of periodontal disease diagnosis and lung cancer incidence in the Women's Health Initiative Observational Study. Cancer Causes & Control. 2014;25(8):1045-53.

36. Arora M, Weuve J, Fall K, Pedersen NL, Mucci LA. An exploration of shared genetic risk factors between periodontal disease and cancers: a prospective co-twin study. Am J Epidemiol. 2010;171(2):253-9.

37. Irfan UM, Dawson DV, Bissada NF. Epidemiology of periodontal disease: a review and clinical perspectives. J Int AcadPeriodontol. 2001;3(1):14.

38. Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. J. Periodontol. 2013;84:S51-69.

39. Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. Cancer causes & control. 2008 ;19(9):895-907.

40. Bergström J, Eliasson S, Dock J. A 10-year prospective study of tobacco smoking and periodontal health. J Periodontol. 2000;71(8):1338-47.

41. Ren HG et.al, Oral health and risk of colorectal cancer: results from three cohort studies and a meta-analysis. Ann Oncol. 2016;27(7):1329-36.

42. Division of Oral Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Disparities in Oral Health.

43. Albandar JM. Global risk factors and risk indicators for periodontal diseases. Periodontol 2000. 2002;29(1):177-206.

44. Chrysanthakopoulos NA. Reasons for extraction of permanent teeth in Greece: a five-year follow-up study. Int Dent J. 2011;61(1):19-24.

45. Lwanga SK, Lemeshow S, World Health Organization. Sample size determination in health studies: a practical manual. WHO; 1991.

46. Machuca G, Segura-Egea JJ, Jiménez-Beato G, Lacalle JR, Bullón P. Clinical indicators of periodontal disease in patients with coronary heart disease: A 10 years longitudinal study. Medicina oral, patologia oral y cirugiabucal. 2012;17(4):e569.

47. Rubin H. Fields and field cancerization: the preneoplastic origins of cancer: asymptomatic hyperplastic fields are precursors of neoplasia, and their progression to tumors can be tracked by saturation density in culture. Bioessays. 201;33(3):224-31.

48. Molloy J, Wolff LF, Lopez-Guzman A, Hodges JS. The association of periodontal disease parameters with systemic medical conditions and tobacco use. J Clin Periodontol. 2004;31(8):625-32.

49. Cutress TW, Ainamo J, Sardo-Infirri J. The community periodontal index of treatment needs (CPITN) procedure for population groups and individuals. Int Dent J. 1987;37(4):222-33.

50. Yoon HS et.al, Association of oral health with lung cancer risk in a low-income population of African Americans and European Americans in the Southeastern United States. Lung Cancer. 2019;127:90-5.

51. Gasperino J. Gender is a risk factor for lung cancer. Medical hypotheses. 2011;76(3):328-31.

52. James A et.al, Higher lung cancer incidence in young women than young men in the United States. N Engl J Med. 2018;378(21):1999-2009.

53. GLOBOCAN 2000. Cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5. Version 1.0.1 [online database]. Lyon, International Agency for Research on Cancer, 2001.

54. Kozielski J, Kaczmarczyk G, Porębska I, Szmygin-Milanowska K, Gołecki M. Lung cancer in patients under the age of 40 years. Contemp Oncol (Pozn). 2012; 16(5): 413-5

55. Thun MJ et.al, Lung cancer death rates in lifelong nonsmokers. J Natl Cancer Inst. 2006;98(10):691-9.

56. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M. Comparative Risk Assessment collaborating group (Cancers. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. The Lancet. 2005;366(9499):1784-93.

57. Clément-Duchêne C, Gauchotte G, Martinet Y, Vignaud JM, Paris C. Lung cancer in patients before the age of 45: A retrospective analysis of 62 patients.

58. Venuta F, Diso D, Onorati I, Anile M, Mantovani S, Rendina EA. Lung cancer in elderly patients J Thorac Dis. 2016 ; 8(Suppl 11): S908-S14

59. Bravo-IñiguezC, PerezMartinez M, ArmstrongKW, JaklitschMT. Surgicalresectionof lung cancer in the elderly. Thorac Surg Clin. 2014;24(4):371-81.

60. Newman C, Takei HH, Klokkevold PR. Epidemiology of Gingival and Periodontal Disease. Plaque control. Clinical Periodontology 8th Ed. USAWB Saunders Company. 1996;64:67-8.

61. Belpomme D et.al, The multitude and diversity of environmental carcinogens. Environ Res. 2007;105(3):414-29.

62. López-Otín C, Blasco MA. L Serrano M Kroemer G. The hallmarks of aging. Cell. 2013;153:1194-217.

63. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. cell. 2011;144(5):646-74.

64. Niccoli T, Partridge L. Ageing as a risk factor for disease. Curr. Biol. 2012;22(17):R741-52.

65. Vijg J, Suh Y. Genome instability and aging. Annu Rev Physiol. 2013;75(1):645-68.

66. Zheng W et.al, Lung cancer and prior tuberculosis infection in Shanghai. Br J Cancer. 1987;56(4):501-4.

67. Hinds MW, Cohen HI, Kolonel LN. Tuberculosis and lung cancer risk in nonsmoking women. Am J Respir Crit Care Med. 1982;125(6):776-8.

68. Hovanec J et.al, Lung cancer and socioeconomic status in a pooled analysis of case-control studies. PloS one. 2018;13(2):e0192999.

69. Aldrich MC et.al, Socioeconomic status and lung cancer: unraveling the contribution of genetic admixture. Am J Public Health. 2013;103(10):e73-80.

70. Ekberg-Aronsson M, Nilsson PM, Nilsson JÅ, Pehrsson K, Löfdahl CG. Socio-economic status and lung cancer risk including histologic subtyping—a longitudinal study. Lung cancer. 2006;51(1):21-9.

71. Hart CL, Hole DJ, Gillis CR, Smith GD, Watt GC, Hawthorne VM. Social class differences in lung cancer mortality: risk factor explanations using two Scottish cohort studies. Int J Epidemiol. 200;30(2):268-74.

72. Mao Y, Hu J, Ugnat AM, Semenciw R, Fincham S. Socioeconomic status and lung cancer risk in Canada. Int J Epidemiol. 2001;30(4):809-17.

73. Clegg LX et.al, Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. Cancer causes & control. 2009;20(4):417-35.

74. Van der Heyden JH et.al, Socioeconomic inequalities in lung cancer mortality in 16 European populations. Lung cancer. 2009;63(3):322-30.

75. Hrubá F et.al, Socioeconomic indicators and risk of lung cancer in Central and Eastern Europe. Eur J Public Health. 2009;17(3):115-21.

76. Sharpe KH et.al, Socioeconomic inequalities in incidence of lung and upper aero-digestive tract cancer by age, tumour subtype and sex: a population-based study in Scotland (2000–2007). Cancer Epidemiol. 2012;36(3):e164-70.

77. Braaten T, Weiderpass E, Kumle M, Lund E. Explaining the socioeconomic variation in cancer risk in the Norwegian Women and Cancer Study. Cancer Epidemiol Biomarkers Prev. 2005;14(11):2591-7.

78. Schaap MM, van Agt HM, Kunst AE. Identification of socioeconomic groups at increased risk for smoking in European countries: looking beyond educational level. Nicotine Tob Res. 2008;10(2):359-69.

79. Sidorchuk A et.al, Socioeconomic differences in lung cancer incidence: a systematic review and meta-analysis. Cancer Causes & Control. 2009;20(4):459.

80. Menvielle G et.al, The role of smoking and diet in explaining educational inequalities in lung cancer incidence. J Natl Cancer Inst. 2009;101(5):321-30.

81. Barbeau EM, Krieger N, Soobader MJ. Working class matters: socioeconomic disadvantage, race/ethnicity, gender, and smoking in NHIS 2000. Am J Public Health. 2004;94(2):269-78.

82. Cokkinides V et.al, Tobacco control in the United States recent progress and opportunities. CA Cancer J Clin. 2009;59(6):352-65.

83. Baquet CR, Horm JW, Gibbs T, Greenwald P. Socioeconomic factors and cancer incidence among blacks and whites. JNCI: J Natl Cancer Inst. 1991;83(8):551-7.

84. Devesa SS, DIAMOND EL. Socioeconomic and racial differences in lung cancer incidence. Am J Epidemiol. 1983;118(6):818-31.

85. Brenner H, Savitz DA, Jöckel KH, Greenland S. Effects of nondifferential exposure misclassification in ecologic studies. Am J Epidemiol. 1992;135(1):85-95.

86. Åstrøm A, Rise J. Socio-economic differences in patterns of health and oral health behaviour in 25 year old Norwegians. Clin Oral Investig. 2001;5(2):122-8.

87. Mouw T et.al, Education and risk of cancer in a large cohort of men and women in the United States. PloS one. 2008;3(11):e3639.

88. Hemminki K, Li X. Level of education and the risk of cancer in Sweden. Cancer Epidemiol Biomarkers Prev. 2003;12(8):796-802.

89. Louwman WJ, van Lenthe FJ, Coebergh JW, Mackenbach JP. Behaviour partly explains educational differences in cancer incidence in the south-eastern Netherlands: the longitudinal GLOBE study. Eur J Cancer prev. 2004;13(2):119-25.

90. Faggiano F, Partanen T, Kogevinas M, Boffetta P. Socioeconomic differences in cancer incidence and mortality. IARC scientific publications. 1997(138):65-176.

91. Faggiano F, Zanetti R, Costa G. Cancer risk and social inequalities in Italy. J Epidemiol Community Health. 1994;48(5):447-52.

92. Bromen K, Pohlabeln H, Jahn I, Ahrens W, Jöckel KH. Aggregation of lung cancer in families: results from a population-based case-control study in Germany. Am J Epidemiol. 2000;152(6):497-505.

93. Schwartz AG. Genetic predisposition to lung cancer. Chest. 2004;125(5):86S-9S.

94. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. Br J Cancer. 2005;93(7):825-33.

95. Chen LS, Kaphingst KA. Risk perceptions and family history of lung cancer: differences by smoking status. Public health genomics. 2011;14(1):26-34.

96. Schwartz AG. Lung cancer: family history matters. Chest. 2006;130(4):936-7.

97. Coté ML et.al, Increased risk of lung cancer in individuals with a family history of the disease: a pooled analysis from the International Lung Cancer Consortium. Eur J Cancer. 2012;48(13):1957-68.

98. Bailey-Wilson JE et.al, A major lung cancer susceptibility locus maps to chromosome 6q23–25. Am J Hum Genet. 2004;75(3):460-74.

99. Denholm Ret al, Is Previous RespiratoryDisease a Risk Factor for Lung Cancer? Am J Respir Crit Care Med. 2014; 190(5): 549-59.

100. Brenner DR et.al, Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. Am J Epidemiol. 2012;176(7):573-85.

101. Papi A et.al, COPD increases the risk of squamous histological subtype in smokers who develop non-small cell lung carcinoma. Thorax. 2004;59(8):679-81.

102. Young RP, Hopkins RJ. Link between COPD and lung cancer. Respir Med. 2010;104(5):758-9.

103. Barnes PJ, Adcock IM. Chronic obstructive pulmonary disease and lung cancer: a lethal association.

104. Houghton AM. Mechanistic links between COPD and lung cancer. Nat Rev Cancer. 2013;13(4):233-45.

105. Liu Z, He X, CHAPMAN RS. Smoking and other risk factors for lung cancer in Xuanwei, China. Int J Epidemiol. 1991;20(1):26-31.

106. Daniels CE, Jett JR. Does interstitial lung disease predispose to lung cancer?Curr Opin Pulm Med. 2005;11(5):431-7.

107. Le Jeume I et.al, The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis inthe UK. Respir Med. 2007; 101: 2534-40.

108. LittmanAJ et.al,Chlamydia pneumoniainfection andrisk of lung cancer. Cancer Epidemiol Biomarkers Prev. 2004;13(10):1624-30.

109. Offenbacher S. Periodontal diseases: pathogenesis. J Periodontol. 1996;1(1):821-78.

110. Mai X et.al, History of periodontal disease diagnosis and lung cancer incidence in the Women's Health Initiative Observational Study. Cancer Causes & Control. 2014;25(8):1045-53.

111. Chrysanthakopoulos NA. Correlation between periodontal disease indices and lung cancer in Greek adults: A case—control study. J Exp Clin Cancer Res. 2016(38,№ 1):49-53.

112. Wen BW et.al, Cancer risk among gingivitis and periodontitis patients: a nationwide cohort study. QJM. 2014;107(4):283-90.

113. Güven DC et.al, Evaluation of cancer risk in patients with periodontal diseases. Turk J Med Sci. 2019;49(3):826-31.

114. Michaud DS et.al, Periodontal disease assessed using clinical dental measurements and cancer risk in the ARIC study. JNCI. 2018;110(8):843-54.

115. Ansai T et.al, Association between tooth loss and orodigestive cancer mortality in an 80-year-old community-dwelling Japanese population: a 12-year prospective study. BMC public health. 2013;13(1):814.

116. Rad M, Kakoie S, Brojeni FN, Pourdamghan N. Effect of long-term smoking on whole-mouth salivary flow rate and oral health. J Dent Res Dent Clin Dent Prospects. 2010;4(4):110.

117. Signorello LB et.al, Southern community cohort study: establishing a cohort to investigate health disparities. J Natl Med Assoc. 2005;97(7):972.

118. Nair J, Ohshima H, Nair UJ, Bartsch H. Endogenous formation of nitrosamines and oxidative DNA-damaging agents in tobacco usersCrit Rev Toxicol. 1996;26(2):149-61.

119. Whitmore SE, Lamont RJ. Oral bacteria and cancer. PLoSPathog. 2014;10(3):e1003933.

120. Cai Q et.al, Association of oral microbiome with lung cancer risk: Results from the Southern Community Cohort Study.121.

121. Yan X et.al, Discovery and validation of potential bacterial biomarkers for lung cancer. Clin Cancer Res. 2015;5(10):3111.

122. Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. Cancer causes & control. 2008;19(9):895-907.Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence. J Periodontol. 2013;84:S8-19.