SUNTEXT REVIEWS

SunText Review of Dental Sciences
ISSN: 2766-4996

Open Access
Research Article
Volume 6:1

Periodontal Condition, Number of Missing Teeth, and Risk of Hodgkin's Lymphoma Development in a Greek Adult Population: A Case-Control Study

Chrysanthakopoulos NA[1,*] and Vazintari V[2]

[1]*Dental Surgeon (DDSc), Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, and University of Athens, Greece*
[2]*MD, Registrar in Pathology, Ilioupoli Health Centre - NHS of Greece, Athens, Greece*

[*]**Corresponding author:** Dr. Chrysanthakopoulos NA, Dental Surgeon (DDSc), Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, and University of Athens, Greece; E-mail: nikolaos_c@hotmail.com, nchrysant@med.uoa.gr

Received date: 13 December 2025; **Accepted date:** 16 December 2025; **Published date:** 22 December 2025

Citation: Chrysanthakopoulos NA, Vazintari V (2025) Periodontal Condition, Number of Missing Teeth, and Risk of Hodgkin's Lymphoma Development in a Greek Adult Population: A Case-Control Study. SunText Rev Dental Sci 6(1): 188.

DOI: https://doi.org/10.51737/2766-4996.2025.188

Abstract

Introduction: Hodgkin's Lymphoma (HL) is a lymphoma type which affects the lymphatic system. Lymphomas are often divided into HLs and non-Hodgkin Lymphomas, whereas two distinct types have also been defined, Classic HL (CHL), and Nodular Lymphocyte-Predominant HL (NLPHL). The aim of the present research was to estimate the possible role of conventional Periodontal Disease (PD) indices, number of missing teeth and the risk of developing CHL.

Methods: This retrospective case-control study was consisted of 98 individuals suffering from CHL and 196 matching healthy ones, who were recruited from one Dental and two Medical private practices, clinically examined and completed a self-administered health questionnaire. The clinical variables assessed the periodontal condition for CHL patients and healthy individuals concerned Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Gingival Index (GI), and number of missing teeth. Statistical analysis was conducted using Univariate and Logistic Regression models adjusted for possible confounders.

Results: Male individuals (p= 0.018, OR= 1.976) with a CHL family history (p= 0.000,OR= 6.366), having an EBV infection history (p=0.022, OR=2.366), with worse PPD(p= 0.043, OR= 1.416), and worse CAL (p=0.033, OR=1.477), were statistically significantly associated with the risk of CHL developing, compared to healthy individuals, after controlling for smoking, educational and socio-economic status.

Conclusion: The current research suggested positive associations of male's individuals with CHL family history, EBV infection history, deeper periodontal pockets, and mode-rate/severe attachment loss, with CHL development.

Keywords: Classic Hodgkin's Lymphoma; Periodontal dsease; Risk factors; Adults

Introduction

Hodgkin lymphoma (HL), also known as Hodgkin disease, is an infrequent monoclonal lymphoid neoplasm which is divided into two distinct categories, Classical Hodgkin Lymphoma (CHL) and Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLP-HL) [1]. CHL represents approximately 95% of all HL cases, and it is further subdivided into four subtypes, Lymphocyte-Rich (LRHL), Nodular Sclerosis (NSHL), Mixed Cellularity (MCHL), and Lymphocyte-Depleted (LDHL). Its histological presentation con-sisted of dispersed large mononuclear Hodgkin and multinucleated Reed-Sternberg cells on a non-neoplastic inflammatory cells background, and characteristic neoplastic cells are frequently surrounded by T lymphocytes [2]. The incidence of CHL subtypes is nodular sclerosis classical Hodgkin lymphoma (70%), mixed cellularity classical HL (25%), lymphocyte-rich

classical Hodgkin lymphoma (5%), and lymphocyte-depleted classical HL (less than 1%). NLPHL accounts for approximately 5% of Hodgkin lymphoma in general [1]. The tumor usually affects young adults, and males, with an estimated incidence rate of 2.6 cases per 100,000 individuals, and represents 11% of all lymphoma cases diagnosed in the United States. It affects ages between 20 to 40 years old, whereas another peak from age 55 years and older, has been recorded [2,3]. The most common subtype in young adults is Nodular sclerosis Hodgkin lymphoma, whereas mixed cellularity Hodgkin lymphoma seems to affect older individuals [1]. HL is one of the most common hematological malignancies of unknown etiology, how-ever possible risk factors concern male gender, low socio-economic status SES), HL fa-mily history, Epstein-Barr (EBV) and Human Immunodeficiency Virus (HIV) infections, auto-immune diseases, and immuno-suppression, and occupational exposure to atmospheric pollutants [1-3]. Prognosis depends on several prognostic factors, such as disease stage. The 5-year overall survival (OS) in stage 1 or 2a is approximately 90%, whereas stage 4 disease has a 5year OS of approximately 60% [4]. PD and mainly the severe type, periodontitis, is a chronic inflammatory disease which affects supporting tissues of tooth, and is responsible for bacterial infection of gingival tissue and surrounding bone structure tissues of teeth [5]. PD as a chronic inflammatory reaction to the dental plaque pathogenic bacteria [6] might lead to systemic inflammation, by increased several inflammatory biomarkers levels in blood circulation, such as IL-6, C-reactive protein (CRP) [7] among patients with periodontitis. The Global Burden of Disease (GBD) Study 2019 recorded approximately 1.1 billion cases of severe periodontitis in 2019, a number that has nearly doubled since 1990 [8]. PD has also been associated with diverse diseases, such as diabetes mellitus (DM) [9], cardiovascular diseases (CVD) [10], rheumatoid arthritis [11], and several types of cancer [12-16], due to possible shared factors [9,13,16,17]. In the last few decades, it has become growingly essential to investigate the relationship between PD and various types of cancer, as it has been associated with a total cancer and certain location-specific cancers elevated risk [17,18]. The association between inflammation and cancer development was suggested by R. Virchow, in 1863 when, following the observation of leukocytes in neoplastic tissues, hypothesized that chronic inflammation could contribute to the tumorigenic process. In the following years, several reports proposed a strong association between chronic inflammation and increased susceptibility to malignant transformation and cancer development. It was estimated that up to 20% of all tumors arise from conditions of persistent inflammatory response such as chronic infections or autoimmune diseases [19]. However, controversial results have been reported, even after controlling for potential confounders such as smoking status, SES, etc. In contrast to the mentioned articles, no previous studies have investigated the possible role of PD as a risk factor for CHL development. Previous studies have examined the possible role of PD and risk of hematopoietic cancers, and found strong and/or marginally significantly associations with an increased risk of developing hematopoietic malignancies, such as Non Hodgkin Lym-phoma (NHL), leukemias, and Multiple Myelomas (MMs) but no with CHL [18,20-29].The mechanism for the mentioned association remains to be elucidate, however, possible mechanisms by which periodontitis increases the cancer risk are inflammation mediators which enter the blood circulation, pathogen invasion into the blood circulation, and host's Immuno-suppression [30,31]. Periodontal bacteria could potentially translocate extra orally in saliva via ingestion, and could infect esophagus [32] or colonic tissues [33], or by aspiration could locate in the respiratory tract [34]. Periodontal bacteria have been identified in lung aspirates [34], lymph nodes [35], arteries [36], precancerous colon [37], gastric [38] lesions, and colorectal [39] and esophageal cancers [40], and may promote a proper microenvironment which can facilitate cancer progression [33,37, 41]. A recent study has focused into the molecular mechanisms which links periodontitis with hematologic diseases [42], and highlights the role of proteomic changes in PD patients and their systemic effects, as it emphasizes how proteins implicated in inflammation, immune response, and tissue regeneration are differentially expressed in PD, potentially impacting hematologic health. Proteomic analysis has detected that chronic periodontitis induces systemic inflammation characterized by elevated levels of proinflammatory cytokines such as IL-6 and CRP, as already mentioned. These inflammatory markers can affect hematopoiesis, resulting in alterations in blood cell production and function, which are crucial in patients with hematologic diseases like anemia and leukemia. Similar recent studies reported that some viruses such as human papilloma, cytomegalic- virus and Epstein Barr present in periodontal pockets and in dental plaque [35,43] are implicated in oral cancer etiology. Epstein - Barr virus (EBV) is considered to be associated with Burkitt lymphoma, HL, nasopharyngeal carcinoma, and gastric cancer. No previous prospective or retrospective epidemiological studies have been carried out in Greece for investigating the possible association between PD indices, number of missing teeth and risk of CHL development. The aim of the present case-control research was to explore the possible association between PD variables, number of missing teeth and risk of CHL development in a sample of Greek adult population.

Materials and Methods

Study Design and Sample Size Determination Study size determination was evaluated according to CHL prevalence and the

EPI-TOOLS guidelines (https://epitools.ausvet.com.au) [44] defined with 95% Confidence Interval (CI) and desired power 0.8. That procedure led to a study size of 294 individuals, 160 males and 134 females aged 20-65 years, 98 suffered from CHL-cases and 196 healthy individuals -controls, who recruited from two medical and a dental private practice between March 2024 and October 2025. CHL patients and healthy participants were undergone an oral clinical examination, and completed an administered medical and dental health questionnaire. The World Health Organization (WHO) recommendations for evaluating periodontal condition incidence were used for estimating age group [45].

Cases and Controls Inclusion/Exclusion Criteria

To be eligible, CHL patients and healthy individuals, should not have been given any periodontal conservative or surgical treatment in the last six months, or prescribed for systemic glucocorticoids or immunosuppression agents or systemic antibiotic regimens within the previous six months, and they should also have more than 20 teeth and suffering from periodontitis (stage I to IV) [46]. From the study protocol were excluded those who suffered from systemic diseases or disorders such as diabetes mellitus (DM), cardiovascular disease (CVD), acute pulmonary diseases, or any other type of malignancies as those conditions could possibly influence oral and periodontal tissues [47] and could lead to biased secondary associations. Cases and controls were selected from the same friendly and collegial environment, were resident of the same city, and were presented to routine health follow-up at the mentioned practices. Members of the same family were excluded from both groups. In an effort to eliminate potential selection biases, healthy individuals were matched for age and smoking habits, as those variables [48] are essential risk factors for periodontitis, and may act as co-variates [49]. The mentioned preconditions were established the initial diagnosis of HL can only be made by performing a lymph node biopsy. Fine needle aspiration (FNA) or core needle biopsies are inadequate because the architecture of the lymph node is extremely important for an accurate diagnosis. CHL is a unique malignancy in that the tumor cells constitute the cellular population minority and an inadequate biopsy may fail to include malignant cells in the specimen. To confirm the diagnosis, it is necessary to reveal the malignant reed Sternberg cell, which is of follicu-Lar center b-cell origin, within the appropriate cellular environment of normal reactive Lymphocytes, eosinophils and histiocytes [50]. Advanced stages chl patients under medical treatment (chemotherapy, radiation theraPy, immunotherapy or targeted therapy), and hospital patients were excluded from the Study protocol.

Data Collection and Intra-Oral Examination

Cases and controls completed a modified Medical Questionnaire [47] by Minnesota Dental School. The collected data concerned the medical/dental history and epidemiology parameters, such as age, gender, smoking status, SE, and educational status, and parameters which could be considered as risk factors for CHL development, such as a CHL family history, previous infection by EBV, presence or absence of auto-immune disease [1-3]. Several auto-immune conditions have been strongly associated with HL development, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), sarcoidosis, and immune thrombocytopenic purpura (ITP) [51]. For the treatment of the above-mentioned diseases systemic glucocorticoids or immuno-suppression agents are prescribed, however the protocol included individuals who appeared CHL within six months after initial diagnosis of those auto-immune diseases. Cases and controls' age was classified as 20-30, 31-40, 41-50, 51-60, 61+, educational status as elementary level and graduated from University/College, socio-economic status as ≤ 1,000 and > 1,000 €/ month, and cigarette smoking status was classified as never (individuals who smoked < 100 cigarettes during their lifetime), and former (individuals Who smoked at least 100 cigarettes in their lifetime and reported that they now smoke "not at all")/current smokers (individuals who smoked at least 100 cigarettes in their life time and reported they now smoke "every day" or "some days"). The periodontal examinations were performed in a dental clinic using a Williams (with a controlled force of 0.2N (DB764R, Aesculapius AG &Co. KG) periodontal probe, mouth mirror, and dental light source. Third molars and remain roots were excluded from scoring. The oral and dental examination concerned the periodontal health condition and focused on probing pocket depth (PPD), clinical attachment loss (CAL), and gingival index (GI). All PD indices were assessed at four sites per tooth (mesiolingual, mesiobuccally, dentilingual, and distobuccally) in all quadrants and the worst values of the indices recorded to the nearest 1.0 mm, and coded as dichotomous variables. PPD was classified as PPD stage I [maximum PPD ≤ 4.0 mm] and stage II-IV [PPD ≤ 4.0 - ≥ 6.0 mm] [46], CAL severity was classified as mild, 1-2.0 mm of attachment loss and moderate/severe, ≥3.0 mm of attachment loss [52]. Gingival inflammation severity was coded as follows: score 0: gingival tissue normal situation and/or mild gingival inflammation, which corresponds to Loe and Silness [53] classification as score 0 and 1, respectively, and -score 1: moderate/severe gingival inflammation which corresponds to the mentioned classification as score 2 and 3, respectively. The number of missing teeth was coded as none, 1-4, 5-10, >10 missing teeth [54]. For establishment of the intra-examiner variance the same was examined a randomly selected sample of 60 (20%) patients and healthy individuals, by the same Dental Surgeon after three weeks, and no differences were observed after the clinical examination (Cohen's Kappa = 0.98).

No oral hygiene instructions were given to the participants during the period of three weeks.

Ethical Consideration

In Greece only experimental studies, such as clinical trials, etc. must be approved by Authorities, such as Health Ministry, Health Organizations, etc. The present research was a retrospective case-control study and was not reviewed and approved by the mentioned Authorities. The individuals who agreed to take part in the present research study obtained an informed consent form.

Statistical Analysis

A univariate model was applied for estimating the association between the independent variables investigated and the risk of CHL development. Categorical data were presented as frequencies and percentages. Socio-demographic factors (age, SE and educational status), comorbidities (family history of CHL, previous infection by EB virus, presence/ absence of auto-immune disease), self-reported variables (smoking habits), were analyzed using the mentioned model. A multivariate logistic regression model was applied (Enter, and Stepwise step) to assess the possible associations among the indices investigated, after adjustment for possible confounders. Unadjusted and adjusted Odds Ratios (OR's), and 95% CI (Confidence Interval) were also assessed. Statistical analysis was performed using SPSS statistical package (SPSS PC20.0, SPSS, Inc., Chicago, IL, USA), and a p value less than 5% ($p < 0.05$) was deemed to be statistically significant.

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

Variables	Cases No %	Controls No %	p-value	Odds Ratio and 95% Confidence Interval
Gender				
Males	58 (59.2)	102 (52.0)	0.246	1.336 (0.818-2.183)
Females	40 (40.8)	94 (48.0)		
Age				
20-30	25 (25.5)	35 (17.9)	0.227	_____
31-40	17 (17.3)	37 (18.9)		
41-50	12 (12.2)	40 (20.4)		
51-60	24 (24.5)	54 (27.6)		
>61	20 (20.4)	30 (15.3)		
Socio-economic status				
Low	55 (56.1)	88 (44.9)	0.069	1.570 (0.963-2.558)
High	43 (43.9)	108 (55.1)		
Education level				
Low	53 (54.1)	99 (50.5)	0.813	1.088 (0.543-2.178)
High	45 (45.9)	97 (49.5)		
Auto-immune disease				
Absence	86 (87.8)	171 (87.2)	0.901	1.048 (0.502-2.188)
		25 (12.8.)		

Presence	12 (12.2)			
CHL family history				
Absence	61 (62.2)	55 (28.1) 141 (71.9)	**0.000***	4.227 (2.529-7.064)
Presence	37 (37.8)			
Cigarette Smoking				
Never	35 (35.7)	90 (45.9) 106 (54.1)	0.095	1.528 (0.927-2.519)
Previous/Current	63 (64.3)			
Previous EBV infection				
Absence	40 (40.8)	115 (58.7) 81 (41.3)	**0.004***	2.059 (1.257-3.371)
Presence	58 (59.2)			
Probing pocket depth (PPD)				
≤ 4.00 mm	38 (38.8)	105 (53.6) 91 (46.4)	**0.017***	0.549 (0.335-0.889)
≤ 4.0 - ≥ 6.0 mm	60 (61.2)			
Clinical Attachment Loss (CAL)				
Absence/Mild: 1.00-2.00 mm	33 (33.7)	101 (51.5) 95 (48.5)	**0.004***	0.478 (0.288-0.790)
Moderate/Severe: ≥ 3.0 mm	65 (66.3)			
Gingival Index (GI)				
Absence/Mild Inflammation	48 (49.0)	104 (53.1) 92 (46.9)	0.509	1.178 (0.725-1.913)
Moderate/Severe Inflammation	50 (51.0)			
Tooth Loss				
None	12 (12.2)	19 (9.7) 65 (33.2)	0.696	_____
1-4 Teeth	37 (37.8)	68 (34.7) 44 (22.4)		
5-10 Teeth	29 (29.6)			
> 10 Teeth	20 (20.4)			

* p-value : statistically significant

Table 2: *Presentation of association between potentially risk factors and BGC according to Enter (first step-1a) and Wald (laststep 8a) method of multivariate logistic regression analysis model.*

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Gender	,669	,294	5,192	1	**,023***	1,952	1,098	3,470
	Age.groups	,011	,100	,012	1	,913	,989	,813	1,204
	EB.history.inf	,495	,303	3,699	1	**,062***	1,884	1,120	2,288
	HL.family.hist	1,724	,321	28,897	1	**,000***	5,605	2,990	10,509
	Autoimm.dis	,109	,297	,134	1	,714	1,073	,363	1,851
	Socioecom.stat	-,066	,286	,054	1	,817	,936	,534	1,641
	Educ.level	-,258	,294	,771	1	,380	,772	,434	1,375
	Cigar.smok	,348	,229	1,243	1	,122	1,115	1,623	1,997
	Prob.Poc.Depth	,604	,301	4,030	1	**,045***	1,829	1,214	2,297
	Clin.Att.Loss	,664	,312	4,527	1	**,043***	1,942	1,154	2,579
	Ging.Index	,229	,307	,556	1	,456	1,257	,689	2,296
	Numb.Miss.Teeth	,255	,159	2,586	1	,108	,775	,568	1,057
	Constant	1,955	,552	12,547	1	,000	,141		
Step 8[a]	Gender	,681	,288	5,581	1	**,018***	1,976	1,123	3,477
	EB.history.inf	,669	,292	5,259	1	**,022***	2,366	1,512	3,501
	HL.family.hist	1,851	,301	37,929	1	**,000***	6,366	3,532	11,473
	Prob.Poc.Depth	,597	,295	4,080	1	**,043***	1,416	1,118	2,241
	Clin.Att.Loss	,630	,296	4,526	1	**,033***	1,477	1,251	2,353
	Constant	2,254	,378	35,626	1	,000	,105		
a. Variable(s) entered on step 1: gender, age.groups, EB.history.inf, HL.family.hist, Autoimm.dis, Socioecom.stat, Educ.level, cigar.smok, Prob.Poc.Depth, Clin.Att.Loss, Ging.Index, Numb. Miss. Teeth.									
* p-value : statistically significant									

Results

The mean age of the study sample was 49 ± 2.1 years. Cases consisted of the main type of HL, CHL, as the second type, NLPHL represented an extremely low size. Moreover, regarding the auto-immune diseases of the sample, 37 individuals, 12 cases, and 25 controls appeared such diseases. Eight individuals who suffered from CHL appeared RA, three SLE, and one sarcoidosis, whereas the number of those without CHL were 14, seven, and four, respectively. Table 1 displays the outcomes after application of Univariate analysis, and showed that the presence of a CHL family history, previous EBV infection, deeper periodontal pockets (PPD), and moderate/severe attachment loss (CAL) were statistically significantly associated with risk for CH development. Table 1 also shows Unadjusted OR's and 95% CI for each variable analyzed. After application of the first step (step 1a -Enter method) of the regression model it was found that, except the mentioned variables, male gender was significantly associated with risk of CHL appearance (Table 2). Table 2 also presents Adjusted OR's and 95% CI for each variable examined. The final step (step 8a – Wald method) of multivariate regression analysis model method showed (Table 2) that males (p=0.018, OR=1.976, 95% CI= 1.123-3.477), previous EBV infection (p=0.022, OR= 2.366, 95% CI=1.512-3.501), CHL family history (p=0.000, OR=6.366, 95% CI= 3.532-1.473), deeper periodontal pockets (p= 0.043, OR=1.416, 95% CI= 1.118-2.241), and moderate/severe attachment loss (p= 0.033, OR= 1.477, 95% CI= 1.251-2.353), were statistically significantly associated with risk for developing CHL, after adjusting for known confounders.

Discussion

The last decades the association between PD, gingivitis and mainly periodontitis, and cancer risk has been explored, leading in most cases in conflicting outcomes. PD as a chronic inflammatory

disease has been associated with diverse systemic diseases and disorders [55-58]. A great amount of research studies has investigated the association between oral health status and various types of cancers. Most reported that periodontitis or the number of missing teeth were associated with an increased risk of several cancers in diverse populations [13,17,59-64]. However, those associations have little practical significance as prevention indices [15], even though useful aspects have been provided on the role of PD treatment in decreasing the risk of different types of cancers [65]. The current report showed that conventional risk factors for CHL development, such as age, SES, educational level, cigarette smoking, and presence of auto-immune diseases were not significantly associated with and increased risk for CHL appearance. Those observations were not in agreement with the outcomes of previous researches, in which adolescents and young adults [2,3,66], low SES and educational level [2,3,67], cigarette smoking [2,3,68], and presence of diseases such as RA, SLE, sarcoidosis, and ITP [51,69-74], were at a higher risk of CHL. Moreover, epidemiological parameters such as age, SES, educational level, and smoking have been considered as confounders. Presence of a CHL family history and history of previous EBV infection were found to be statistically significantly associated with the risk of CHL development among the indices investigated, findings which were in accordance with those from previous reports [1,2,66]. The outcomes also showed that deep periodontal pockets, expressed by PPD and moderate/severe attachment loss, expressed by CAL were significantly associated with risk of developing CHL, findings that were not confirmed by previous studies, as the available ones have investigated the mentioned possible association for hematopoietic malignancies such as Acute Myeloid (AM) and Lymphoblastic Leukemia (ALL), the Chronic ones (CML, CLL), their diverse variants, and NHL. PPD is used for estimating PD severity [75], as is a current disease inflammation status indicator [76], and CAL is a critical index for estimating cumulative periodontal tissue destruction, including previous PD attacks. The mentioned indices concern the chronic inflammation long-term stages including the chronic inflammatory response destructive signs [77]. Gingival inflammation, as expressed by GI and number of missing teeth were also not statistically associated with risk of CHL development, in the current study. Similarly, no previous studies have examined the mentioned possible associations. GI reflects gingival inflammation severity, nevertheless that index is not used regularly in epidemiological studies regardless of that estimates the gingival tissues inflammatory load. A specific role has been suggested for gingival inflammation as a risk factor for diverse cancer types [78], whereas other researchers observed no relationships [79,80]. Tooth loss is the advanced periodontitis final outcome. Previous prospective studies have recorded an association between number of missing teeth and the cancer risk in various locations [18, 80, 81]. Similarly, case-control surveys, have recorded powerful links between tooth loss and pancreatic [15], upper gastrointestinal [82], lung [83], gastric [84], esophageal [85], oral [83], and ovarian [62] cancers.

The mechanism which is implicated in cancer development in PD patients is still remain unclear. An hypothesized role of immune-inflammatory mechanisms and inflammation in both periodontitis and cancer has been suggested [18]. The periopathogenic bacteria and their by-products associated with chronic periodontitis can lead to chronic systemic inflammation [86,87] not only at the oral tissue but even at distant locations [88]. That periodontal bacteria accumulation has been detected at local or distant locations, are able to infiltrate through infected periodontal tissues into the systemic circulation and reach those distant locations [87], such as various organs and tissues, lymph nodes [35], arteries [36,89] etc. At the target location, periodontal pathogens may create an appropriate micro-environment which is able to contribute to cancer progression [14,37,41]. Inflammation is a cancer hallmark [90], and PD is an infectious process that induces chronic low-grade inflammation and, persistent low-grade inflammation has been associated with cancer initiation [19,91,92]. Inflammatory response can generate Reactive Oxygen Species (ROS) and active intermediates producing oxidative/ nitrosative stress, which may lead to DNA mutations, or they may affect the DNA repair mechanisms [93]. The inflammatory cells may further contribute to the cells damage by producing ROS, cytokines, chemokines, and arachidonic acid metabolites. Those products recruit various inflammatory cells and maintain a vicious cycle [93]. Periopathogenic bacteria such as Porphyromonas gingival is and Aggregatibacter actinomycetemcomitans are anaerobic, gram-negative bacteria which colonize sub gingival biofilms in periodontitis patients [94]. Those bacteria produce and release enzymes which deconstruct the extra-cellular matrix ingredients including collagen, process that leads to substrates production which increase tissue invasion [95]. The released bacterial endotoxins, enzymes, and metabolic by-products are toxic to tissues, may cause direct damage to neighboring epithelial cells DNA, and they can induce mutations in proto-oncogenes and tumor suppressor genes, or alterations in molecular signaling pathways involved in cell survival, differentiation or proliferation [96]. Oral bacteria may also induce carcinogenesis by constitutively activating toll-like receptors (TLRs), such as TLR5 [95]. TLR5s are present on the innate immune system cells surfaces, have been associated with epithelial and cancer cells [97] and are implicated in proliferation, inflammation, invasion, and anti-tumor immune responses evasion [98,99]. Porphyromonas gingival is and Fusobacterium nucleatum can promote tumor progression by activating TLRs on oral epithelial cells to up-regulate the IL-

6/STAT3 signaling pathway [100]. PD may also increase cancer risk through the chronic release of inflammatory mediators or immune system dysregulation [19, 101-103], or may affect carcinogenesis through the increased exposure to carcinogenic nitrosamines [104]. Oral bacteria and nitrosamines generation is increased in oral cavity in individuals with poor oral hygiene and PD [62]. Consequently, anti-inflammation therapy in PD individuals reduces the systemic inflammation biomarkers and may decrease subsequent cancer risk. On the contrary, Hwang, et al. [65] recorded that anti-inflammation treatment did not reduce the lymphatic and hematopoietic cancers risk. Tooth loss was found to be positively associated with risk of certain cancers such as head and neck, esophageal, and lung cancers [62], as mentioned. Moreover, a dose response meta-analysis reported that each ten-tooth loss was associated with a 3% increase of risk of hematopoietic cancer [105]. Periodontal bacteria may contribute to carcinogenesis by influencing cell proliferation and activation of nuclear factor NF-κB and inhibiting apoptosis [106]. PD plaque is in many cases not under reasonable control, driving periodontal bacteria to disseminate and accumulate in some locations of the human organism through the digestive or respiratory tract, or endocrine system, contributing to cancer development [107-109]. Oral bacteria in the blood circulation, particularly their lipopolysaccharide component (LPS), can induce systemic inflammatory responses [110]. Inflammatory mediators released from chronic PD, such as Il-6, tumor necrosis factor-alpha (TNF-α), and prostaglandin E2 (PGE2), can escape through damaged periodontal tissue pockets and produce systemic effects in the whole organism [111]. Recent epidemiological studies have investigated the risk of hematopoietic and lymphatic cancers in individuals with periodontitis [18,30,112-115]. However, these studies resulted in contradictory outcomes. Chronic periodontitis could lead to increased risks of hematological cancers [112], and severe PD was associated with a two-fold higher risk of hematological cancers, including leukemia and other hematological cancers [113]. Michaud, et al. [18] confirmed such an association even after controlling for smoking and other risk factors, as was observed that PD was found to be statistically significant-ly associated with an increased risk of hematopoietic cancers, whereas among never smokers, PD was associated with statistically significantly increases in hematopoietic cancers. Similar researches revealed no association between PD and hematopoietic malignancies, such as leukemia's and lymphatic cancers [30,114,115]. As shown, few previous and recent reports have observed an increased risk of AML, ALL and other hematopoietic malignancies development among individuals with PD however, considerable limitations of those included inadequate sample sizes and adjustment for potential confounders. The strengths and limitations of the current research should be taken into account in interpretation of the observed outcomes. Strengths of the study are the completeness of follow-up, the well-characterized cohort which it was possible to examine both confounding and interaction by known risk factors, in order to avoid secondary biased associations. Another critical aspect is PD definition by oral clinical examination and not by self-report, therefore no potential misclassification of exposure to PD exists that may result in the underestimation of the association examined. Another limitation is the possibility of confounding in estimates of risk caused by additional unknown confounders.

Conclusions

The present study showed that males with a family CHL history, a history of previous EBV infection, with deep periodontal pockets (PPD), and moderate/severe attachment loss (CAL) were significantly associated with an increased risk of developing CHL.

References

1. Lees C, Keane C, Gandhi MK, Gunawardana J. Biology and therapy of primary mediastinal B-cell lymphoma: current status and future directions. Br J Haematol. 2019; 185: 25-41.
2. Metzger ML, Mauz Korholz C. Epidemiology, outcome, targeted agents and immunonotherapy in adolescent and young adult non Hodgkin and Hodgkin lymphoma. Br JHaematol. 2019; 185:1142-1157.
3. Huang Junjie, Sze Pang Wing, Lok Veeleah, Zhang Lin, Lucero Prisno III Don Eliseo, et al. Incidence, mortality, risk factors, and trends for Hodgkin lymphoma: a global data analysis. J Hematol Oncol. 2022; 15:57
4. Chihara D, Oki Y, Fanale MA, Westin JR, Nastoupil LJ, Neelapu S, et al. Stage I non Hodgkin lymphoma: no plateau in disease-specific survival ? Ann Hematol. 2019; 98: 1169-1176.
5. Huang Y, Michaud DS, Lu J. The association of clinically determined periodontal disease and edentulism with total cancer mortality: the National Health and Nutrition Examination Survey III. Int J Cancer. 2020; 147: 1587-1596.
6. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005; 366: 1809-1820.
7. Moutsopoulos NM, Madianos PN. Low-grade inflammation in chronic infectious diseases: paradigm of periodontal infections. Ann NY Acad Sci. 2006; 1088: 251-264.
8. Wu L, Zhang SQ, Zhao L, Ren ZH, Hu CY. Global, Regional, and National Burden of Periodontitis from 1990 to 2019: Results from the Global Burden of Disease Study 2019. J Periodontol. 2022; 93: 1445-1454.
9. Kebede TG, Holtfreter B, Kocher T, Meisel P,Dietrich T, Biffar R, et,al. Association of Periodontal Destruction and Diabetes with Mortality. J Dent Res. 2017; 96: 56-63.
10. Demmer RT, Desvarieux M. Periodontal infections and cardiovascular disease: the heart of the matter. J Am Dent Assoc. 2006; 137 (Suppl): 14S-20S. Quiz 38S.

11. Beydon M, Pinto S, De Rycke Y, Fautrel B, Mariette X, Seror R, et al. Risk of cancer for patients with rheumatoid arthritis versus general population: a national claims database cohort study. Lancet Reg Health Eur. 2023; 35:100768.
12. Gao S, Li S, Ma Z, Liang S, Shan T, Zhang M, et al. Presence of Porphyromonas gingivalis in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Inf Agent Canc. 2016; 11:3.
13. Chen Y, Zhu BL, Wu CC, Lin R-F, Zhang X. Periodontal Disease and tooth loss are Associated with Lung Cancer Risk. Biomed Res Int. 2020; 5107696.
14. Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling viaits FadA adhesion. Cell Host Microbe. 2013; 14:195-206.
15. Fitzpatrick SG, Katz J. The association between periodontal disease and cancer: a review of the literature. J Dent. 2010; 38: 83-95.
16. Babic A, Pool EM, Terry KL, Cramer DW, Teles RP, Tworoger ST. Periodontal bone loss and risk of epithelial ovarian cancer. Canc Caus Control. 2015; 26: 941-947.
17. Michaud DS, Fu Z, Shi J, Chung M. Periodontal Disease, tooth loss, and Cancer Risk. Epidemiol Rev. 2017; 39:49-58.
18. 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. Lanc Oncol. 2008; 9: 550-558.
19. Coussens LM, Zena Werb. Inflam Canc. Nature. 2002; 420: 860-867
20. Chrysanthakopoulos NA, Vryzaki E. Investigation of the Association between Periodontal Disease Indices and Risk of Acute Hematopoietic Cancer Development (Acute Myeloid and Acute Lymphoblastic Leukemia): A Case-Control Study. Sumerianz J Med Health, 2022; 5: 9-17.
21. Guven DC, Dizdar O, Akman AC, Berker E, Yekedüz E, Ceylan F, et al. Evaluation of cancer risk in patients with periodontal diseases. Turk J Med Sci. 2019; 49: 826-831.
22. Huang L-G, Yu C-C, Lin M-C, Wang Y-H, Chang Y-C. Association between Periodontitis and Hematologic Cancer: An NHIRD Cohort Study in Taiwan. Cancers. 2024; 16: 1671.
23. Kim EH, Nam S, Park CH, Kim Y, Lee M, Ahn JB, et al. Periodontal disease and cancer risk: A nationwide population-based cohort study. Front Oncol. 2022; 12: 901098.
24. Barton Kay M. Evidence Accumulates Indicating Periodontal Disease as a Risk Factor for Colorectal Cancer or Lymphoma. CA Cancer J Clin. 2017; 67: 173-174.
25. Wu Y, Shi X, Li Y, Xia Ju, Gu Y, Qian Q, et al. Hematopoietic and lymphatic cancers in patients with periodontitis: a systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2020; 25: e21-28.
26. Lobacz M, Mertowska P, Mertowski S, Kozinska A, Kwasniewski W, Kos M, et al. The Bloody Crossroads: Interactions between Periodontitis and Hematologic Diseases. Int J Mol Sci. 2024; 25: 6115.
27. Haozhen Ma, Jianmao Zheng, Xiaolan Li. Potential risk of certain cancers among patients with Periodontitis: a supplementary meta-analysis of a large-scale population. Int J Med Sci. 2020; 17: 2531-2543.
28. Dinachandran A, Padmakumar TP, Devisree RV, Pillai HB, Sudhakar A. Periodontitis as a risk factor for cancer. IP Int J Periodontol Implantol. 2022; 7: 48-51.
29. Kimberly AB, Shingala J, Evens A, Birmann BM, Giovannucci E, Michaud DS. Periodontal disease and risk of non-Hodgkin lymphoma in the Health Professionals Follow-up Study. Int J Cancer. 2017; 140: 1020-1026.
30. Michaud DS, Jiayun Lu, Peacock-Villada AY, Barber JR, Joshu CE, Prizment AE, et al. Periodontal Disease Assessed Using Clinical Dental Measurements and Cancer Risk in The ARIC Study. J Natl Cancer Inst. 2018; 110: 843-854.
31. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015; 15: 30-44.
32. Nwizu N, Wactawski-Wende J, Genco RJ. Periodontal Disease and Cancer: Epidemiologic Studies and Possible Mechanisms. Periodontol 2000. 2020; 83: 213-233.
33. Arora M, Weuve J, Fall K, Pedersen NL, Mucci LA. An Explo ration of Shared Genetic Risk Factors between Periodontal Disease and Cancers: A Prospective CoTwin Study. Am J Epidemiol. 2010; 171: 253-259.
34. Bartlett JG, Gorbach SL, Finegold SM. The bacteriology of aspiration pneumonia. Am J Med. 1974; 56: 202-207.
35. Amodini Rajakaruna G, Umeda M, Uchida K, Furukawa A, Yuan B, Suzuki Y, et al. Possible translocation of periodontal pathogens into the lymph nodes draining the oral cavity. J Microbiol. 2012; 50: 827-836.
36. Gaetti-Jardim E Jr, Marcelino SL, Feitosa AC, Romito GA, Avila-Campos MJ. Quantitative detection of periodontopathic bacteria in atherosclerotic plaques from coronary arteries. J Med Microbiol. 2009; 58: 1568-1575.
37. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumorimmune microenvironment. Cell Host Microbe. 2013; 14: 207-215.
38. Salazar CR, Sun J, Li Y, Francois F, Corby P, Perez-Perez G, et al. Association between selected oral pathogens and gastric pre-cancerous lesions. PLoS One. 2013; 8: 51604.
39. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012; 22: 299-306.
40. Narikiyo M, Tanabe C, Yamada Y, Igaki H, Tachimori Y, Kato H, et al. Frequent and pre-ferential infection of Treponema denticola, Streptococcus mitis, and Streptococcus anginasus in esophageal cancers. Cancer Sci. 2004; 95: 569-574.
41. Perera M, Al-Hebshi NN, Speicher DJ, Perera I, Johnson NW. Emerging role of bacteria in oral carcinogenesis: a review with special reference to periopathogenic bacteria. J Oral Microboil. 2016; 26:32762.
42. Reckelkamm SL, Kaminska I, Baumeister SE, Holtfreter B, Alayash Z, Rodakowska E, Baginska J, Kaminski KA, Nolde M. Optimizing a Diagnostic Model of Periodontitis by Using Targeted Proteomics. J. Proteome Res. 2023; 22: 2509-2515.

43. Piemonte ED. Relationship between chronic trauma of the oral mucosa, oral potentially malignant disorders and oral cancer. J Oral Pathol Medic. 2010; 39: 513-517.
44. Villarta RL, Asaad AS. Sample Size Determination in an Epidemiologic Study using the EpiTools Web-Based Calculator. Acta Med Phil. 2014; 48: 42-46.
45. World Health Organization. Oral health surveys: basic methods. Geneva: World Health Organization; 1997.
46. Tonetti MS, Greenwell H, Kornman KS. Staging and Grading of Periodontitis: Framework and Proposal of a New Classification and Case Definition. J Periodontol. 2018; 89: S159-S172.
47. Machuca G, Segura-Egea JJ, Jimenez-Beato G, Lacalle JR, Bullón P. Clinical indicators of periodontal disease in patients with coronary heart disease: A10 years longitudinal study. Med Oral Patol Oral Cir Bucal. 2012; 17: e569-574.
48. Tonetti MS, Claffey N. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. J Clin Periodontol. 2005; 32: 210-213.
49. Loos BG, John RP, Laine ML. Identification of genetic risk factors for periodontitis and possible mechanisms of action. J Clin Periodontol. 2005; 32: 159-179.
50. Ansell SM. Hodgkin lymphoma: 2025 update on diagnosis, risk-stratification, and management. Am J Hematol. 2024; 99: 2367-2378.
51. Kristinsson SY, Landgren O, Sjoberg J, Turesson I, Bjorkholm M, Goldin LR, et al. Autoimmunity and risk for Hodgkin's lymphoma by subtype. Haematologica. 2009; 94:1468-1469.
52. Wiebe CB, Putnins EE. The periodontal disease classification system of the American academy of periodontology an update. J Can Dent Assoc. 2000; 66: 594-597.
53. Loe H. The Gingival Index, the Plaque Index, and the Retention Index Systems. J Periodontol. 1967; 38: 610-616.
54. Yoon HS, Wen W, Long J, Zheng W, Blot WJ, 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: 90-95.
55. Blaizot A, Vergnes J-N, Nuwwareh S, Amar J, Sixou M. Periodontal Diseases and Cardiovascular Events: Meta-Analysis of Observational Studies. Int Dent J. 2009; 59: 197-209.
56. De Oliveira Ferreira R, de Brito Silva R, Barauna Magno M, Carvalho Almeida APCPS, Fernandes Fagundes NC, Cople Maia L, et al. Does Periodontitis Represent A Risk Factor for Rheumatoid Arthritis? A Systematic Review and Meta-Analysis. Ther AdvMusculoskelet. 2019; 11: 1759720X19858514.
57. Moghadam SA, Shirzaiy M, Risbaf S. The associations between periodontitis and respiratory disease. J Nepal Health Res Counc. 2017; 15: 1-6.
58. Helenius-Hietala J, Suominen AL, Ruokonen H, Knuuttila M, Puukka P, Jula A, et al. Periodontitis Is Associated with Incident Chronic Liver Disease-A Population Based Cohort Study. Liver Int. 2019; 39: 583-591.
59. Zeng X-T, Ling-Yun X, Yong-Gang Z, Sheng Li, Leng W-D, Kwong JSW. Periodontal Disease and Incident Lung Cancer Risk: A Meta-Analysis of Cohort Studies. J Periodontol. 2016; 87: 1158-1164.
60. Al-Maweri SA, Wael Ibraheem I, Al-Ak'hali MS, Shamala A, Halboub E, Nasser Al-hajj M. Association of Periodontitis and Tooth Loss with Liver Cancer: A Systematic Review. Rev Oncol Hematol. 2021; 159: 103221.
61. Chen H, Nie S, Zhu Y, Lu M. Teeth Loss, Teeth Brushing and Esophageal Carcinoma: A Systematic Review and Meta-Analysis. Sci Rep. 2015; 5: 15203.
62. Hiraki A, Keitaro M, Takeshi S, Kazuo T. Teeth Loss and Risk of Cancer At 14 Common Sites in Japanese. Cancer Epidem Biomar. 2008; 17: 1222-1227.
63. Lee K, Ji Sung L, Jinkwon K, Huisong L, Chang Y, Geol Woo H, et al. Oral Health and Gastrointestinal Cancer: A Nationwide Cohort Study. J Clin Periodontol. 2020; 47: 796-808.
64. Momen-Heravi F, Babic A, Tworoger SS, Zhang L, Wu K, Smith-Warner SA, et al. Periodontal Disease, Tooth Loss and Colorectal Cancer Risk: Results from The Nurses' Health Study. Int J Cancer. 2017; 140: 646-652.
65. Hwang I-M, Li-Min S, Cheng-Li L, Chia-Hung K. Periodontal Disease with Treatment Reduces Subsequent Cancer Risks. QJM. 2014; 107: 805-812.
66. Punnett A, Tsang RW, Hodgson DC. Hodgkin lymphoma across the age spectrum: epidemiology, therapy, and late effects. Semin Radiat Oncol. 2010; 20: 30-44.
67. Landgren O, Engels EA, Pfeiffer RM, Gridley G, Mellemkjaer L, Olsen JH, et al. Autoimmunity and susceptibility to Hodgkin lymphoma: a population-based casecontrol study in Scandinavia. J Natl Cancer Inst. 2006; 98(18): 1321-1330.
68. Hjalgrim H, Melbye M, Lagiou P. Hodgkin lymphoma. Text Cancer Epidemiol. Chapter 26. 2018; 627-648.
69. Hollander P, Rostgaard K, Smedby KE, Chang ET, Amini RM, de Nully Brown P, etal. Autoimmune and atopic disorders and risk of classical Hodgkin Lymphoma. Am J Epidemiol. 2015; 182: 624-632.
70. Kedra J, Seror R, Dieude P, Constantin A, Toussirot E, Kfoury E, et al. Lymphoma complicating rheumatoid arthritis: results from a French case-control study. RMD Open. 2021; 7: e001698.
71. Fallah M, Liu X, Ji J, Forsti A, Sundquist K, Hemminki K. Hodgkin lymphoma after autoimmune diseases by age at diagnosis and histological subtype. Ann Oncol. 2014; 25: 1397-1404.
72. Bernatsky S, Ramsey-Goldman R, Isenberg D, Rahman A, Dooley MA, Sibley J etal. Hodgkin's lymphoma in systemic lupus erythematosus. Rheumatol (Oxford). 2007; 46: 830-832.
73. Anderson LA, Gadalla S, Morton LM, Landgren O, Pfeiffer R, Warren JL, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. Int J Cancer. 2009; 125: 398-405.
74. Smedby KE, Hjalgrim H, Askling J, Chang ET, Gregersen H, Porwit-MacDonald A, et al. Autoimmune and chronic inflammatory disorders and risk of non-hodgkin lymphoma by subtype. J Natl Cancer Inst. 2006; 98(1): 51-60.
75. Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol. 1996;1: 1-36
76. Burt B. Position paper: epidemiology of periodontal diseases. J Periodontol. 2005; 76: 1406-1419.

77. Miskiewicz A, Szparecki G, Durlik M, Rydzewska G, Ziobrowski I, Gorska R. The correlation between pancreatic dysfunction markers and selected indices of periodontitis. Adv Clin Exp Med. 2018; 27: 313-319.
78. Beger-Luedde J, Loosen SH, Luedde T, Roderburg C, Kostev K. Association between Chronic Gingivitis and Cancer: A Retrospective Cohort Study of 19,782 Outpatients from the United Kingdom. Cancers (Basel). 2023; 15: 2007.
79. Meurman JH, Kallmen H, Andersson LC, YucelLindberg T, Söder B. Prevalence of cancer in relation to signs of periodontal inflammation. Plos One. 2022; 17: e0276375.
80. Virtanen E, Soder P-O, Meurman JH, Andersson LC, Soder B. Chronic Periodontal Disease: A Proxy of Increased Cancer Risk. Int J Canc Res. 2013; 47: 1127-1133.
81. 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: 171-175.
82. Abnet CC, Qiao Y-L, Dawsey SM, Dong Z-W, Taylor PR, Mark SD. 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: 467-474.
83. Sadighi Shamami M, Sadighi Shamami M, Amini S. Periodontal Disease and Tooth Loss as Risks for Cancer: A Systematic Review of the Literature. Iran J Cancer Prev. 2011; 4:189- 198.
84. Abnet CC, Kamangar F, Dawsey SM, Stolzenberg Solomon RZ, Albanes D, Pietinen P, 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: 681-687.
85. Rosenquist K. Risk factors in oral and oropharyngeal squamous cell carcinoma: a population- based case control study in southern Sweden. Swed Dent J Suppl. 2005; 179:1-66.
86. Amabile N, Susini G, Pettenati-Soubayroux I, Bonello L, Gil J-M, Arques S.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: 644-652.
87. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol. 2005; 76: 2106- 2115.
88. Hayashi C, Gudin CV, Gibson FC, Genco CA. 2010. Pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specificinnate immune inflammatory pathways. Mol Oral Microbiol. 2010; 25: 305-316.
89. Ford PJ, Gemmell E, Chan A, Carter CL, Walker PJ, Bird PS. Inflammation, heat shock proteins and periodontal pathogens in atherosclerosis: an immune-histologic study. Oral Microbiol Immunol. 2006; 21: 206-211.
90. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646- 674.
91. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001; 357: 539-545.
92. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008; 454: 436-444.
93. Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer. 2007; 121: 2381-2386.
94. Page RC. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. Ann Periodontol. 1998; 3: 108-120.
95. Kauppila JH, Mattila AE, Karttunen TJ, Salo T. Toll-like receptor 5 (TLR5) expression is a novel predictive marker for recurrence and survival in squamous cell carcinoma of the tongue. Br J Cancer. 2013; 108: 638-643.
96. Anil S, Varma SV, Preethanath RS, Anand PS, Al-Farraj AA. The emerging concepts on the impact of periodontitis on systemic health. Interchopen. 2012: 121-164.
97. Kauppila JH, Mattila AE, Karttunen TJ, Salo T. Toll like receptor 5 and the emerging role of bacteria in carcinogenesis. Oncoimmunology. 2013; 2: e23620.
98. Basith S, Manavalan B, Yoo TH, Kim SG, Choi S. Roles of toll like receptors in cancer: a double-edged sword for defense and offense. Arch Pharm Res. 2012; 35: 1297-1316.
99. Park JH, Yoon HE, Kim DJ, Kim SA, Ahn S G, Yoon JH. Toll like receptor 5 activation promotes migration and invasion of salivary gland adenocarcinoma. J Oral Pathol Med. 2011; 40: 187-193.
100. Gallimidi A, Fischman S, Revach B, Bulvik R, Maliutina A, Rubinstein A. Periodontal pathogens Porphyromonas gingivalis and Fusobacterium nucleatum promote tumor progression in an oral specific chemical carcinogenesis model. Oncotarget. 2015; 6: 22613-22623.
101. Grulich AE, Vajdic CM, Cozen W. Altered immunity as a risk factor for non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2007; 16: 405-408.
102. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell. 2006; 124: 823-835.
103. Vendrame E, Hussain SK, Breen EC, Magpantay LI, Widney DP, Jacobson LP. Serum levels of cytokines and biomarkers for inflammation and immune activation, and HIV-associated non Hodgkin B-cell lymphoma risk. Cancer Epidemiol Biomarkers Prev. 2014; 23: 343-349.
104. Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. Canc Caus Control. 2008; 19: 895-907.
105. Shi J, Leng W, Zhao L, Deng C, Xu C, Wang J. Tooth loss and cancer risk: a dose response meta-analysis of prospective cohort studies. Oncotarget. 2018; 9: 15090-15100.
106. Taniguchi K, Karin M. NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol. 2018; 18: 309-324.
107. Ma X, Chi C, Fan L, Dong B, Shao X, Xie S, et al. The Microbiome of Prostate Fluid Is Associated With Prostate Cancer. Front Microbiol. 2019; 10: 1664.
108. Shao J, Wu L, Leng WD, Fang C, Zhu Y-J, Jin Y-H, et al. Periodontal Disease and Breast Cancer: A MetaAnalysis of 1,73,162 Participants. Front Oncol. 2018; 8: 601.

109. Zhang Y, Sun C, Song EJ, Liang M, Shi T, Min M, et al. Is periodontitis a risk indicator for gastrointestinal cancers? A meta-analysis of cohort studies. J Clin Periodontol. 2020; 47: 134-147.
110. Pussinen PJ, Tuomisto K, Jousilahti P, Havulinna AS, Sundvall J, Salomaa V. Endotoxemia, Immune Response to Periodontal Pathogens, And Systemic Inflammation Associate with Incident Cardiovascular Disease Events. Arterioscler Thromb Vasc Biol. 2007; 27: 1433-1439.
111. Loos B. Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients. J Periodontol. 2000.
112. Chung SD, Tsai MC, Huang CC, Kao LT, Chen CH. A population-based study on the associations between chronic periodontitis and the risk of cancer. Int J Clin. Oncol. 2016; 21: 219- 223.
113. Mai X, La Monte MJ, Hovey KM, Freudenheim JL, Andrews CA, Genco RJ. Periodontal diseaseseverity and cancer risk in postmenopausal women: the Buffalo Osteo Perio Study. Canc Caus Control. 2016; 27; 217-228.
114. Nwizu NN, Marshall JR, Moysich K, Genco RJ, Hovey KM, Mai X. Periodontal disease and incident cancer risk among postmenopausal women: Results from the women's health initiative (whi) observational cohort. Canc Epidemiol Biomark. Prev. 2017; 26: 1255-1265.
115. Wen BW, Tsai CS, Lin CL, Chang YJ, Lee CF, Hsu CH. Cancer risk among gingivitis and periodontitis patients: a nationwide cohort study. QJM. 2014; 107: 283-290.