Investigation of the Association Between Periodontal Disease Indices, Number of Missing Teeth and Risk of Thyroid Cancer Development: A Case – Control Study

Abstract

Objective: To investigate the possible association between PD clinical parameters, and number of missing teeth and the risk of developing Thyroid Cancer (TC) in Greek adults using a population-based retrospective cohort database.

Materials and Methods: A total of 45 TC patients-cases and 90 age and gender-matched non-TC individuals - controls were recruited from one Dental and two Medical private practices. A dental clinical examination and a standardized questionnaire were used to collect the following clinical parameters Probing Pocket Depth (PPD), Gingival Index (GI), Clinical Attachment Loss (CAL), Bleeding on Probing (BOP), the number of missing teeth and the dependent and independent risk factors for TC development. Statistical analysis was conducted using Univariate and Logistic Regression models adjusted for possible confounders.

Results: Statistical analysis showed that TC family history (p= 0.049, OR=2.081, 95% CI= 0.658-4.122), and BOP (p =0.053, OR= 1.698, 95% CI= 0.538-2.109), were statistically significantly associated with the risk of TC developing.

Conclusion: The current investigation suggested positive associations of Thyroid Cancer Family History, and Bleeding on Probing with Thyroid Cancer development.

Keywords

Thyroid cancer • Periodontal disease • Risk factors • Adults

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Introduction

Thyroid Cancer (TC) is the most common endocrine cancer nowadays worldwide [1,2], as its incidence has increased all over the world in the last three decades [1,3]. However, TC is a relatively rare neoplasia, accounting for 0.35%-0.38%of total deaths due to cancer in Greece [4], whereas recent data [5] showed that the lowest estimated incidence ASR-E were recorded in Montenegro (2.2), FYR Macedonia (2), and Albania, Bosnia and Herzegovina and Greece (1.9). According to the Main Diagnostic groups of the 2022 WHO Classification of Thyroid Neoplasms seven types of Malignant Thyroid Neoplasms have been recorded,

Follicular Thyroid Carcinoma (FTC), Oncocytic Thyroid Carcinoma (OTC), Invasive Encapsulated Follicular Variant Papillary Thyroid Carcinoma (IEFvPTC), Papillary Thyroid Carcinoma (PTD), Differentiated High-Grade Thyroid Carcinoma (DhgTC), Poorly Differentiated Thyroid Carcinoma (PDTC),and Anaplastic Thyroid Carcinoma (ATC) [6]. However, the two main differentiated types are the Papillary and Follicular types and consist about 95% of all TCs. Anaplastic TC is uncommon as accounts for about 1% of TC [1,7], and Medullary TC (MTC) is present in 3-5% of all thyroid carcinomas [7]. The two main types of Periodontal Disease (PD), are gingivitis and periodontitis. PD is a chronic, multifactorial, and immunological disease that affects periodontal tissues [8,9]. Gingivitis is a gingiva reversible inflammation and concerns soft tissue surrounding the teeth whereas periodontitis is characterized by periodontal tissues irreversible loss and eventually leads to tooth loss [10].

Gingivitis progresses to periodontitis in susceptible individuals with compromised immune system [8,9]. PD prevalence has been assessed 20-50% globally, whereas a proportion of 10% of the population worldwide has been affected by severe periodontitis [10-12]. In the United States 42.2% of dentate adults aged 30 years or older suffer from periodontitis, whereas 7.8% of the mentioned individuals suffer from severe periodontitis [13]. TC appearance has been associated with diverse genetic and environmental/ nutritional factors, as the precise causes of TC development are still unknown [3]. Potential risk factors for TC concern high risk factors such as radiation exposure (especially in head and neck region), chromosomal (genetic) alterations, and hereditary conditions (hereditary MTC, Non-syndromic and syndromic Familial non-Medullary TC), and low risk factors that concern thyroid imaging with iodine 131, iodine deficiency, high thyroid stimulating hormone (TSH) level, auto-immunity, thyroid nodules, environmental pollutants, smoking, lifestyle, diet, and high Body Mass Index (BMI), whereas the possible role of oestrogens remains unclear [14-31].The association between inflammation and cancer development is well known since 1863 when R. Virchow, following the observation of leukocytes in neoplastic tissues, suggested that chronic inflammation could contribute to the tumorigenic process. In the following years, several researchers 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 [32].

The possible mechanisms by which inflammation can contribute to carcinogenesis includes induction of genomic instability, enhanced proliferation of initiated cells, resistance to apoptosis, alterations in epigenetic events and subsequent inappropriate gene expression, aggressive tumor neovascularization, invasion through tumor-associated basement membrane and metastasis [33]. Inflammation also affects immune surveillance and responses to therapy. Moreover, chronic infection is able to result in unresolved inflammation that has been considered an important factor contributing to cellular transformation, tumorigenesis, and tumor promotion and progression [32,34]. The associations between gastric cancer and *Helicobacter pylori* induced gastritis, cervical cancer and papilloma virus, hepatocellular carcinoma, hepatitis B and C viral infections, esophageal adenocarcinoma and Barrett's metaplasia and many others, are also well known [32]. Similar reports have detected associations between PD, and periodontitis mainly and cancer at different regions in human organism [35-40]. Prospective studies found increases in the overall cancer risk associated with PD of 14% to 24%, and the association was not attenuated even after adjustment for known risk factors, such as age, smoking status, socio-economic status and other confounders [38,40,41].

However, possible conflicting and controversial associations in case of specific cancer types could be attributed to differences in study populations, cohort sizes, study designs, the use of diverse clinical indices to define PD, and the effects of known and unknown confounders. Although the methodology to determine PD was not consistent across studies, those that were investigated large samples showed a consistent relationship between PD and cancer risk, and that risk seemed to increase significantly depending on PD severity [41]. Some of the mechanisms that seem to be responsible for the association between inflammation and cancer, in general, have been recently elucidated. However, the mechanisms through which cancer may be appeared among individuals who suffer from PD are not entirely clear. During inflammatory response several cell types migrate to the sites of tissue damage, and several biomarkers and

signaling pathways initiate and sustain the inflammatory response. The mentioned cells secrete free radicals and active intermediates (ROS and RNI), cytokines (such as TNF, IL-1, IL-6), chemokines, vasoactive, molecules, such as histamine and leukotrienes, metabolites of arachidonic acid, proteases, etc.

Those products are able to cause oxidative/ nitrosative stress, that may result in DNA point mutations in cells, rearrangements and double-strand breaks in the DNA [42], or they may interfere with DNA repair mechanisms [43]. This results in a higher probability of oncogene activation or of tumor suppressor loss of function. The chronic infection of periodontal tissues can cause systemic effects and results in an increased plasma concentration of inflammatory cytokines and chemokines, that are linked to PD severity, such as C reactive protein (CRP), Il-1 and Il-6 [44,45]. An hypothesized role of immunity mechanisms that may be common to both diseases, PD and cancer, has also been suggested [46,47]. The potential mechanism that links periodontitis and cancers in distant locations is probably associated with the persistent periodontal infection and inflammation that are able to induce systemic chronic inflammation, and eventually cancer.

Periodontal pathogens especially *Porphyromonas gingivalis*, and *Fusobacterium nucleatum* have been detected from some orodigestive cancer tissues, indicating that these pathogens may play a role in carcinogenesis and tumor multiplicity at distant locations [48,49]. *P. gingivalis* is could be potentially hepato-carcinogenic in mice [50,51]. Moreover, periodontal treatment can substantially decrease biomarkers of systemic inflammation [45,52] and certain anti-inflammatory drugs such as non- steroidal anti-inflammatory drugs (NSAIDs) may help to prevent or decrease the risk of certain site-specific cancers, such as colorectum, esophagus, stomach, breast, and biliary tract [53,54]. Moreover, a 40-50% reduction in the incidence of colorectal cancer is associated with the regular use of NSAIDs, the COX enzymes that catalyze the synthesis of proinflammatory mediators, such as prostaglandins [55,56].

The role of oral microbiota dysbiosis is another possible mechanism that appears to be implicated in the pathogenesis of both periodontitis and cancer [57,58]. Periodontal tissues or oral mucosa microbiota is involved in cancer pathogenesis and modify the responses to cancer treatment [59,60]. Oral cavity microbiota is connected to the respiratory tract and acts as the entry portal for the gastrointestinal tract, as enter the respiratory and gastro-intestinal tract. Consequently, oral microbiota dysbiosis, mainly in periodontitis, can contribute to cancer development of the gastrointestinal and respiratory tract, such as head and neck squamous cell carcinoma, lung, gastric, pancreatic, and colorectal cancer [61,65]. Therefore, further epidemiologic studies must focus on the investigation of the role of oral microbiome and/ or specific established periodontal pathogens in relation to PD and cancer risk. In Greece previous prospective or retrospective epidemiological studies have not been carried out for investigating the possible association between PD and risk of TC. The aim of the present case-control research was to examine the possible association between PD indices and number of missing teeth and risk of developing TC in a sample of adults in Greece.

Materials and Methods

Research participants and design

The current research was a population-based, retrospective cohort, case-control study using data from one Dental and two Medical private practices obtained between March 2021 and November 2023. Study size evaluation was based on TC prevalence [66] and the EPITOOLS guidelines (https://epitools.ausvet.com.au) determined with 95% Confidence Interval (CI) and desired power 0.8. The World Health Organization (WHO) recommendations for assessing periodontal status incidence were used for assessing age group [67]. That procedure resulted in a study sample of 45 individuals suffered from TC-cases and 90 healthy ones-controls, ages 40 to 80 years.

Cases and controls eligibility criteria

To be eligible, TC patients and healthy individuals, should not have been treated by a periodontal conservative or a surgical process in the last 6 months, or prescribed for systemic glucocorticoids or immunosuppression agents or systemic antibiotic regimens within the previous 6 months, and they should also have more than15 teeth and periodontitis from stage I to IV [68]. Individuals who suffered from systemic diseases or disorders such as cardiovascular disease (CVD), acute pulmonary diseases,

rheumatoid arthritis, diabetes mellitus (DM), or any type of malignancies were excluded from the study protocol as those diseases could potentially affect oral and periodontal tissues [69] 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.

Moreover, they were matched for gender, age, and smoking status, as gender, age, and smoking history are known risk factors for periodontitis development [70]. Advanced TC patients under medical treatment/ metastatic disease, patients with TC metastases of a primary focus at a different location, and hospital patients were excluded from the study protocol. Cases group consisted of individuals whose the TC primary diagnosis was based on patients' medical files and Ultrasound (US) findings, however the definitive diagnosis was confirmed by percutaneous fine needle aspiration (FNA) or core biopsy, most frequently under ultrasound (US) guidance [71]. TC patients include those that suffered from the most common differentiated types, Papillary and Follicular type of TC [1]. The current study was not an experimental one and was not approved by authorized committees (Health Ministry, etc.). All individuals, cases and controls, were informed about the aims/methods and significance of the present study, and gave their written consent to enrol in the study protocol.

Data collection

A well-trained and calibrated Dental Surgeon performed oral and periodontal tissues examinations and the participants completed a modified Medical Questionnaire [72] which contained information concerning their medical and dental history. The mentioned Dental Surgeon performed periodontal examinations in a dental clinic using a Williams (with a controlled force of 0.2N (DB764R, Aesculap AG & Co. KG,) periodontal probe, mouth mirror, dental light source, and tissue forceps, and information about the probing pocket depth (PPD), clinical attachment loss (CAL), gingival index (GI) and bleeding on probing (BOP), as a measure of PD status was obtained. Third molars and remain roots were excluded from scoring. All PD indices were measured at four sites per tooth (mesio-lingual, mesio-buccal, distolingual, and distobuccal) in all quadrants and the worst values of the indices recorded to the nearest 1.0 mm, and coded as dichotomous variables. Probing Pocket Depth (PPD) index was classified as 0-3.00 mm (absence of disease/ mild disease) and ≥ 4.0 mm (moderate and severe disease) for mean PPD [73], attachment loss (CAL) severity was classified as mild, 1-2.0 mm of attachment loss and moderate/severe, ≥ 3.0mm of attachment loss [74], and the number of missing teeth as none, 1-4, 5-10, >10 missing teeth [75].

Gingival Inflammation was determined by the examination of four sites per tooth, and its severity was classified as follows: -score 0: normal situation of gingival tissue and/ or mild gingival inflammation, that corresponds to Löe and Silness [76] classification as score 0 and 1, respectively, and -score 1: moderate/severe gingival inflammation that corresponds to the mentioned classification as score 2 and 3, respectively. The presence/absence of BOP were recorded and coded as dichotomous variables.

Confounding variables

Confounding factors included demographic parameters, such as age, gender, socio-economic and educational status, lifestyle behaviours, such as smoking history, and BMI, and existence or absence of TC family history. Cases' and Controls' age was classified as 40-49, 50-59, 60-69,70-79, 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 categorized as never smokers (those who smoked<100 cigarettes during their lifetime), and former (those who smoked atleast 100 cigarettes in their lifetime and reported that they now smoke "not at all")/current smokers (those who smoked at least 100 cigarettes in their life-time and reported they now smoke "every day" or "some days"). BMI is an obesity index and was classified as normal (<30 Kg/m^2) and high (≥30 Kg/m^2), and is considered as a risk factor for TC development [77]. The intra-examiner variance was assessed by a sample of 27 (20%) individuals that was chosen randomly and re-examined clinically by the same Dental Surgeon after three weeks, and no significant differences were recorded between the 1st and the 2nd clinical examination (*Cohen's Kappa = 0.97*).

Statistical analysis

Univariate analysis was carried out to compare categorical variables between cases and controls. A multivariable logistic regression model was used to analyze the risk factors for developing TC, adjusting for age, gender, educational, socio-economic, and smoking status. Unadjusted and adjusted Odds Ratios (OR's) and 95% (Confidence Interval) CI were also recorded. Statistical analysis was carried out using SPSS statistical package (SPSS PC20.0, SPSS, Inc., Chicago, IL, USA), and a p value less than 5% ($p < 0.05$) was considered to be statistically significant.

Results

The mean age of the study sample was 56 ± 3.8 years. Cases consisted of the two main types of TC (Papillary and Follicular type), as the remain ones represent an extremely low size. Table 1 presents the outcomes after application of Univariate analysis, and showed that no one of the variables examined was statistically significantly associated with risk for TC development. Table 1 also shows Unadjusted OR's and 95% CI for each variable examined. After performance of the first step (step 1[a]-Enter method) of the regression model it was found that no one of the variables examined was statistically significantly associated with risk for TC development (Table 2). Table 2 also shows Adjusted OR's and 95% CI for each parameter examined. The final step (step 9[a]-Wald method) of multivariate regression analysis model (Table 2) method showed that TC family history (p= 0.049), was statistically significantly associated with risk for developing TC, whereas BOP (p= 0.053) was marginally statistically significantly associated with risk for developing TC.

Discussion

PD as a chronic inflammatory disease has been associated with diverse systemic diseases and disorders [78-81]. Several studies have investigated the association between oral health status and various types of cancers. Most recorded that periodontitis or the number of missing teeth were associated with an increased risk of several cancers in diverse populations [40,62,82-87]. However, those associations have little practical significance as prevention indices [88], even though useful aspects have

been provided on the role of PD treatment in decreasing the risk of different types of cancers [89].

As already mentioned, TC appearance has been associated with diverse genetic and environmental/nutritional factors, as the precise causes of TC development are still unclear [3,14-31,90,91]. No associations were found between common epidemiological parameters such as age, gender, socio-economic status, educational level, and smoking status. Those parameters are also considered as confounders. In the current report TC family history, and BOP were significantly associated with risk of TC. A TC family history is a suggested risk factor in 5-15% of TC cases. Several genetic mutations have identified to be involved in the development of Differentiated TC [92]. Rearranged during transfection (RET) chromosomal rearrangement genes, and RAS or BRAF proto-onco-genes mutation is able to trigger the activation of the mitogen-activated protein kinase (MAPK) cascade in PTC development. Mutations of the BRAF, RAS, or RET genes have been observed in nearly 70% of PTC cases [93,94]. The familial risk of TC represents the highest rate in all cancer sites, for which the increased risk extends beyond the nuclear family [95,96]. However, only few reports have investigated the risk factors of familial history for TC. Most of the studies were focused on familial non-Medullary TC, or the study sample sizes were relatively small [97].

Hwang et al. showed that multi-collinearity existed between Ultrasonography (US) assessment and patient age, and first-degree TC family history and serum thyroid hormone values [97]. A first-degree family history of TC, age, and high TSH levels did not independently significantly increase the risk of TC. The study concluded that a first-degree family history as a risk factor for thyroid malignancy should be further investigated in asymptomatic patients. The bleeding index (BOP) expresses the host's vascular response in relation to hyperemia, the capillaries' dilation and enhanced blood flow in the inflammation region. BOP is a widely used criterion to diagnose gingival inflammation, however it has been detected that periodontal pockets with a probing depth of greater than or equal to 5.00 mm showed a significantly higher incidence of BOP. BOP is also an essential index of periodontal examination and diagnosis, and the most valid PD activity indicator [98]. BOP has not been examined as a PD index for searching the possible association between PD and specific cancers.

Variables	Cases	Controls	p-value	Odds Ratio and 95% Confidence Interval
Gender				
Males	24 (53.3)	50 (55.6)	0.475	0.914 (0.446-1.875)
Females	21 (46.7)	40 (40.8)		
Age				
40-49	8 (17.8)	15 (16.7)		
50-59	12 (26.7)	20 (22.2)	0.930	
60-69	14 (31.1)	27 (30.0)		_____
70-79	6 (13.3)	17 (18.9)		
80+	5 (11.1)	11 (12.2)		
Socio-economic status				
Low	28 (62.2)	58 (64.4)	0.472	0.909 (0.433-1.907)
High	17 (37.8)	32 (35.6)		
Education level				
Low	20 (44.4)	37 (41.1)	0.813	1.088 (0.543-2.178)
High	25 (55.6)	53 (58.9)		
Body Mass Index				
<30 kg/m^2	12 (26.7)	38 (42.2)	**0.056***	0.498 (0.228-1.088)
≥30 kg/m^2	33 (73.3)	52 (57.8)		
TC family history				
Absence	15 (33.3)	39 (43.3)	0.176	0.654 (0.310-1.380)
Presence	30 (66.7)	51 (56.7)		
Smoking				
Never	16 (35.6)	43 (47.8)	0.122	0.603 (0.288-1.261)
Previous/Current	29 (64.4)	47 (52.2)		
Probing pocket depth				
0-3.00 mm	12 (26.7)	35 (38.9)	0.112	0.571 (0.261-1.253)
≥ 4.0 mm	33 (73.3)	55 (61.1)		
Clinical Attachment Loss				
Absence/Mild: 1.00-2.00 mm	14 (31.1)	37 (41.1)	0.173	0.647 (0.303-1.381)
Moderate/Severe: ≥ 3.0 mm	31 (68.9)	53 (58.9)		
Gingival Index				
Absence/Mild Inflammation	10 (22.2)	31 (34.4)	0.103	0.544 (0.238-1.243)
Moderate/Severe Inflammation	35 (77.8)	59 (65.6)		
Bleeding on probing				
Absence	18 (40.0)	32 (35.6)	0.375	1.208 (0.579-2.523)
Presence	27 (60.0)	58 (64.4)		
Number of missing teeth				
None	6 (13.3)	12 (13.3)		
1-4 Teeth	11 (24.4)	23 (25.6)	0.862	
5-10 Teeth	18 (40.0)	30 (33.3)		_____
> 10 Teeth	10 (22.2)	25 (27.8)		

* p-value: statistically significant

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

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	gender	,903	,734	1,514	1	,219	2,468	,585	4,403
	age	,219	,286	,588	1	,443	,803	,458	1,407
	educ.level	,451	,730	,043	1	,536	,860	,206	2,595
	socio-econ	,622	,632	,088	1	,429	,746	,388	1,750
	TC.fam.history	1,139	,824	1,911	1	,087	3,125	,621	4,218
	smoking	,923	,828	1,244	1	,265	1,197	,497	2,043
	body.mass.ind	,174	,782	,050	1	,823	1,240	,581	2,389
	pock.prob.dep	1,706	,924	3,410	1	,095	1,707	,601	2,670
	ging.index	,708	,955	,550	1	,458	1,093	,576	2,191
	clin.att.loss	,968	1,039	,869	1	,351	1,633	,544	2,169
	bleed.prob	1,346	1,028	1,716	1	,090	1,260	,835	2,350
	miss.teeth	,110	,400	,076	1	,783	1,016	,510	1,745
	Constant	2,532	1,648	2,362	1	,124	,079		
Step 9[a]	TC.fam.history	,986	,717	1,895	1	**,049***	2,081	,658	4,122
	bleed.prob	,921	,713	1,671	1	**,053***	1,698	,538	2,109
	Constant	1,726	,871	3,921	1	,048	,178		

a. Variable(s) entered on step 1: gender, age, educ.level, TC.fam.history, smoking, body.mass.ind, pock.prob.dep, ging.index, clin.att.loss, bleed.prob, miss.teeth.

 * p-value: statistically significant

Table 2. Presentation of association between potentially risk factors and TC according to Enter (first step-1a) and Wald (last step 9a) method of multivariate logistic regression analysis model.

Periodontal pockets and CAL refer to the long-term stages of chronic inflammation including destructive processes signs of a chronic inflammatory response [99]. However, no associations were recorded, in the present report, between PPD, GI and CAL and risk of TC development. The mentioned outcomes were not in accordance with those of a previous report [100], in which was observed that both males and females with periodontitis had a higher risk of TC (females: aHR = 1.20, 95% CI = 1.04–1.38; males: aHR = 1.51, 95% CI = 1.15–1.99). Similarly, a recent nationwide cohort study showed that periodontitis patients were associated with an increased risk of TC (aHR=1.191, 95% CI=1.085-1.308, p=0.0002), after adjusting of smoking history. It also recorded that cumulative cancer incidence over time was shown in primary cancer of diverse organs including thyroid, suggesting that periodontitis patients increased overall cancer incidence compared to the control group [101]. Hiraki et al. [85], in another similar study found no association between PD and risk of TC. On the other hand, more, studies have examined the number of missing teeth and risk of cancer in diverse organs. It was also, observed that the decreased number of teeth remaining was associated with lower OR for TC (p=0.127).

In another study Kang et al., recorded that for TC, missing teeth were associated with decreased cancer risk (OR =0.78, 95% CI, 0.7–0.88) [102]. However, the number of TC patients was small, with only 121 of the 5,240 cancer patients included in the study. Therefore, there might be a statistical bias. Moreover, because only individuals with malignancy-suspected thyroid nodules take FNA or biopsy, it is possible that there are pathologically undiagnosed TC cases. Consequently, the results of the study may not reflect the association between missing teeth and the real risk of TC. However, during the follow-up period of the individuals included in this report, the incidence of TC increased significantly to the extent that

this was criticized for over-diagnosis [103]. The reason why individuals with missing teeth showed a significantly lower risk of TC is difficult to be explained, and further research is needed to clarify this. To date, it still remains unclear the mechanism for the link between dental/oral health and cancer, and many hypotheses have been suggested. Some researchers have suggested that inflammation caused by oral bacterial infection can initiate and promote systemic inflammation and systemic inflammatory cytokines, chemokines and other biomarkers, which play a role in initiating malignancies [104,105]. Another possible mechanism is that chronic inflammation caused by oral bacteria can promote local inflammation in surrounding tissues [106, 107].

It can be suggested that dental health status mainly affects the head and neck region, digestive tract, lung, liver, and biliary-pancreas where oral bacteria can reach. This process supports a mechanism of local inflammation and irritation of surrounding tissues by contact with oral bacteria. Indeed, many reports have identified some oral microbiota associated with cancer risk in several organs [108-112]. The destructive inflammation in periodontitis is driven by complement-dependent mechanisms following oral microbial dysbiosis and may spread out of the oral cavity [113]. In periodontitis, bacterial plaque destroys the periodontal epithelial cells and allows the entry of oral pathogens and their products, endotoxins and exotoxins, into the blood circulation, thus inducing systemic inflammation [114,115] which is a crucial factor that facilitates the cancer hallmarks necessary for malignant transformation, including sustaining proliferative signaling, enabling replicative immortality, evading growth suppressors, resisting cell death, inducing angiogenesis, and activating invasion and metastasis [33]. Certain anti-inflammatory drugs, such as NSAIDs, have shown potential in preventing or reducing the risk of specific cancers in certain sites, such as colorectal, esophageal, gastric, biliary tract, and breast cancers. An overall trend of increased cancer risk among patients with PD compared with those without periodontitis, worldwide, has been shown [35]. A systemic chronic inflammation appears to play a prominent role in those proposed pathways.

Inflammatory responses could result in ROS/RNI production, which might contribute to DNA mutations within cells that interfere with DNA repair mechanisms [43], as already mentioned. In the oral-systemic link, ulcerated periodontal pockets can unintentionally allow toxic metabolites and oral bacteria to enter the blood circulation and affect distant body regions and organs. Oral bacteria in the blood circulation, particularly their lipopolysaccharide component (LPS), can induce systemic inflammatory responses [116]. Inflammatory mediators released from PD, such as Il-6, tumor necrosis factor-alpha (TNF-α), and prostaglandin E2, can escape through damaged periodontal tissue pockets and produce systemic effects in the whole body [117]. Multiple dental X-ray exposures have been associated with an increased risk of TC. It has been suggested that while periodontal treatment may reduce systemic inflammation, patients may still be exposed to dental X-rays, contributing to an overall elevated risk of TC [118]. Risk analysis of TC with missing teeth has rarely been conducted, and there is only one report on the risk of thyroid disease with missing teeth [119], and found no significant association with the risk of TC in that study.

The current study has some interfering factors that should be taken into account in interpretation of the observed outcomes regarding the relation between PD and cancer, in general. Case-control studies have used different criteria in the definition and measurement of PD. Some used the common PD indices, such as PPD, GI, CAL, number of missing teeth and others based on patient history, self-questionnaires, clinical, and radiographic findings as criteria for PD patients [120]. It must also be taken into account that teeth can be lost due to trauma, caries, or PD. Therefore, it is difficult to eliminate trauma and caries as possible confounders [121]. Strengths of the current research are the follow-up completeness, the well-characterized cohort that it was possible to examine both confounding and interaction by known risk factors, in order to avoid referring secondary biased associations. Another essential aspect is PD definition by oral clinical examination and not by self-reported questionnaires, therefore no possible misclassification of exposure to PD exists that may result in the underestimation of the association investigated.

A potential limitation is the possibility of confounding in estimates of risk caused by additional unknown

confounders. Moreover, some environmental factors also seem to be confounders among those studies [122]. Those variables are age, gender, genetic, educational and socioeconomic status as are considered as risk factors for both diseases. Actually, researches which are adjusted for those variables can be used for the estimation of PD as an independent risk factor of cancer [85].

Conclusion

The current research showed that individuals with a Thyroid Cancer family history, and those with presence of Bleeding on Probing were at significantly higher risk for Thyroid Cancer development. Those associations remained after controlling for certain confounders such as socioeconomic, educational, and smoking status. No significant associations were recorded among others epidemiological parameters such as age, gender, socio-economic and educational status, smoking, and Body Mass Index. Therefore, there is a need for further exploration using randomized controlled clinical trials and well-designed, large prospective studies to help clarify the nature of association and, in particular, add evidence to support causality between Periodontal Disease and risk of Thyroid Cancer. Those studies should focus on standardized clinical measurements in ascertaining Periodontal Disease status.

Conflict of Interest

The authors declare that they have no conflict of interests. The study was self-funded by the author and co-Authors.

References

1. Bonnefond, Simon and Terry F. Davies. "Thyroid Cancer—Risks and Causes." *Journal Thyroid Cancer Risks and Causes* (2014).

2. Kusić, Z. "Prgomet D. Carcinoma of The Thyroid and Parathyroid Glands." *Prgomet D. Tumors of the head and neck. Zagreb: Medicinska naklada* (2019): 262-73.

3. Pellegriti, Gabriella, Francesco Frasca, Concetto Regalbuto and Sebastiano Squatrito, et al. "Worldwide Increasing Incidence of Thyroid Cancer: Update on Epidemiology and Risk Factors." *J Cancer Epidemiol* (2013).

4. Ilias, Ioannis, Maria Alevizaki, Elli Lakka-Papadodima and Demetrios A. Koutras. "Differentiated Thyroid Cancer in Greece: 1963-2000. Relation to Demographic and Environmental Factors." *Hormones (Athens, Greece)* 1 (2002): 174-178.

5. European Network of Cancer Registries ENCR Thyroid cancer (TC) Factsheet (2017) https: www. encr.eu/sites/default/files/factsheets/ENCR_ Factsheet_Thyroid_201. 7-2.pdf

6. Juhlin, C. Christofer, Ozgur Mete and Zubair W. Baloch. "The 2022 Who Classification of Thyroid Tumors: Novel Concepts in Nomenclature and Grading." *Endocr Relat Cancer* 30 (2023).

7. Hundahl, Scott A., Blake Cady, Myles P. Cunningham and Ernest Mazzaferri, et al. "Initial Results from A Prospective Cohort Study Of 5583 Cases of Thyroid Carcinoma Treated in The United States During 1996: An American College of Surgeons Commission on Cancer Patient Care Evaluation Study." *Cancer* 89 (2000): 202-217.

8. Kinane, Denis F., Panagiota G. Stathopoulou and Panos N. Papapanou. "Periodontal Diseases." *Nat Rev Dis Primers* 3, (2017): 1-14.

9. Highfield, J. "Diagnosis and Classification of Periodontal Disease." *Aust Dent J* 54 (2009): S11-S26.

10. Peres, Marco A., Lorna MD Macpherson, Robert J. Weyant and Blánaid Daly, et al. "Oral Diseases: A Global Public Health Challenge." *Lancet* 394 (2019): 249-260.

11. Kassebaum, N. J., Eduardo Bernabé, M. Dahiya and B. Bhandari, et al. "Global Burden of Severe Periodontitis In 1990-2010: A Systematic Review and Meta-Regression." *J Dent Res* 93 (2014): 1045-1053.

12. GBD 2017 Oral Disorders Collaborators, E. Bernabe, W. Marcenes, C. R. Hernandez and J. Bailey, et al. "Global, Regional, And National Levels and Trends

in Burden of Oral Conditions From 1990 To 2017: A Systematic Analysis for The Global Burden of Disease 2017 Study." *J Dent Res* 99 (2020): 362-373.

13. Eke, Paul I., Gina O. Thornton-Evans, Liang Wei and Wenche S. Borgnakke, et al. "Periodontitis in Us Adults: National Health and Nutrition Examination Survey 2009-2014." *J Am Dent Assoc* 149 (2018): 576-588.

14. Bonnefond S, Davies TF "Thyroid Cancer-Risks and Causes". *Oncol Hematol Rev* 10 (2014): 14451.

15. Xing, Mingzhao. "Molecular Pathogenesis and Mechanisms of Thyroid Cancer." *Nat Rev Cancer* 13 (2013): 184-199.

16. Caudill, Christy M., Zhaowen Zhu, Raffaele Ciampi and Yuri E. Nikiforov. "Dose-Dependent Generation of Ret/Ptc in Human Thyroid Cells After In vitro Exposure To γ-Radiation: A Model of Carcinogenic Chromosomal Rearrangement Induced by Ionizing Radiation." *J Clin Endocrinol Metab* 90 (2005): 2364-2369.

17. Ron, Elaine, Jay H. Lubin, Roy E. Shore and Kiyohiko Mabuchi, et al. "Thyroid Cancer After Exposure to External Radiation: A Pooled Analysis of Seven Studies." *Radiat Res* 141 (1995): 259-277.

18. Memon, Anjum, Sara Godward, Dillwyn Williams and Iqbal Siddique, et al. "Dental X-Rays and The Risk of Thyroid Cancer: A Case-Control Study." *Acta Oncol* 49 (2010): 447-453.

19. Hieu, Trinh Trung, Anthony W. Russell, Ross Cuneo and Justin Clark, et al. "Cancer Risk After Medical Exposure to Radioactive Iodine in Benign Thyroid Diseases: A Meta-Analysis." *Endocr Relat Cancer* 19 (2012): 645-655.

20. Guan, Haixia, Meiju Ji, Rong Bao, Hongyu Yu and Yangang Wang, et al. "Association of High Iodine Intake with The T1799a Braf Mutation in Papillary Thyroid Cancer." *J Clin Endocrinol Metab* 94 (2009): 1612-1617.

21. Chen, Yen-Kung, Cheng-Li Lin, Yen-Jung Chang and Fiona Tsui-Fen Cheng, et al. "Cancer Risk in Patients with Graves' Disease: A Nationwide Cohort Study." *Thyroid* 23 (2013): 879-884.

22. Vukasović, Anamarija, Sanja Kusačić Kuna, Karmen Trutin Ostović and Drago Prgomet, et al. "Diffuse Sclerosing Variant of Thyroid Carcinoma Presenting as Hashimoto Thyroiditis: A Case Report." *Coll Antropol* 36 (2012): 219-221.

23. Mukasa, Koji, Jaeduk Yoshimura Noh, You Kunii and Masako Matsumoto, et al. "Prevalence of Malignant Tumors and Adenomatous Lesions Detected by Ultrasonographic Screening in Patients with Autoimmune Thyroid Diseases." *Thyroid* 21 (2011): 37-41.

24. Brito, Juan P., Andres J. Yarur, Larry J. Prokop and Bryan McIver, et al. "Prevalence of Thyroid Cancer in Multinodular Goiter Versus Single Nodule: A Systematic Review and Meta-Analysis." *Thyroid* 23 (2013): 449-455.

25. Ward, Mary H., Briseis A. Kilfoy, Peter J. Weyer and Kristin E. Anderson, et al. "Nitrate Intake and The Risk of Thyroid Cancer and Thyroid Disease." *Epidemiol* 21 (2010): 389-395.

26. Zhang, Yawei, Grace L. Guo, Xuesong Han and Cairong Zhu, et al. "Do Polybrominated Diphenyl Ethers (Pbde) Increase the Risk of Thyroid Cancer?" *Biosci Hypotheses* 1 (2008): 195-199.

27. Liang, Jiaxin, Nan Zhao, Cairong Zhu and Xin Ni, et al. "Dietary Patterns and Thyroid Cancer Risk: A Population-Based Case-Control Study." *Am J Transl Res* 12 (2020): 180.

28. Schmid, Daniela, Gundula Behrens, Carmen Jochem and Marlen Keimling, et al. "Physical Activity, Diabetes, And Risk of Thyroid Cancer: A Systematic Review and Meta-Analysis." *Eur J Epidemiol* 28 (2013): 945-958.

29. Kitahara, Cari M., Martha S. Linet, Laura E. Beane Freeman and David P. Check, et al. "Cigarette Smoking, Alcohol Intake, And Thyroid Cancer Risk: A Pooled Analysis of Five Prospective Studies in The United States." *Cancer Causes & Control* 23 (2012): 1615-1624.

30. Derwahl, Michael, and Diana Nicula. "Estrogen and Its Role in Thyroid Cancer." *Endocr Relat Cancer* 21 (2014): T273-T283.

31. Myung, Seung-Kwon, Chan Wha Lee, Jeonghee Lee and Jeongseon Kim, et al. "Risk Factors for Thyroid Cancer: A Hospital-Based Case-Control Study in Korean Adults." *Cancer Res Treat* 49 (2017): 70.

32. Coussens, Lisa M. and Zena Werb. "Inflammation and Cancer." *Nature* 420 (2002): 860-867.

33. Hanahan, Douglas and Robert A. Weinberg. "Hallmarks of Cancer: The Next Generation." *cell* 144 (2011): 646-674.

34. Swann, Jeremy B., Matthew D. Vesely, Anabel Silva and Janelle Sharkey, et al. "Demonstration of Inflammation-Induced Cancer and Cancer Immunoediting During Primary Tumorigenesis." *PNAS* 105 (2008): 652-656.

35. Nwizu, Ngozi, Jean Wactawski-Wende and Robert J. Genco. "Periodontal Disease and Cancer: Epidemiologic Studies and Possible Mechanisms." *Periodontol 2000* 83 (2020): 213-233.

36. Michaud, Dominique S., Yan Liu, Mara Meyer and Edward Giovannucci, et al. "Periodontal Disease, Tooth Loss, And Cancer Risk in Male Health Professionals: A Prospective Cohort Study." *Lancet Oncol* 9 (2008): 550-558.

37. Arora, Manish, Jennifer Weuve, Katja Fall and Nancy L. Pedersen, et al. "An Exploration of Shared Genetic Risk Factors Between Periodontal Disease and Cancers: A Prospective Co-Twin Study." *Am J Epidemiol* 171 (2010): 253-259.

38. Nwizu, Ngozi N., James R. Marshall, Kirsten Moysich and Robert J. Genco, et al. "Periodontal Disease and Incident Cancer Risk Among Postmenopausal Women: Results from The Women's Health Initiative Observational Cohort." *Cancer Epi demiol Biomarkers Prev* 26 (2017): 1255-1265.

39. Michaud, D. S., K. T. Kelsey, E. Papathanasiou and E. Giovannucci. "Periodontal Disease and Risk of All Cancers Among Male Never Smokers: An Updated Analysis of The Health Professionals Follow-Up Study." *Ann Oncol* 27 (2016): 941-947.

40. Michaud, Dominique S., Zhuxuan Fu, Jian Shi and Mei Chung. "Periodontal Disease, Tooth Loss, and Cancer Risk." *Epidemiol Rev* 39 (2017): 49-58.

41. Michaud, Dominique S., Jiayun Lu, Alexandra Y. Peacock-Villada and John R. Barber, et al. "Periodontal Disease Assessed Using Clinical Dental Measurements and Cancer Risk in The ARIC Study." *J Natl Cancer Inst* 110 (2018): 843-854.

42. Colotta, Francesco, Paola Allavena, Antonio Sica and Alberto Mantovani. "Cancer-Related Inflammation, The Seventh Hallmark of Cancer: Links to Genetic Instability." *Carcinogenesis* 30 (2009): 1073-1081.

43. Federico, Alessandro, Floriana Morgillo, Concetta Tuccillo and Carmela Loguercio. "Chronic Inflammation and Oxidative Stress in Human Carcinogenesis." *Int J Cancer* 121(2007): 2381-2386.

44. Renvert, Stefan, Christel Lindahl, Ann-Marie Roos-Jansåker and Jan Lessem. "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* 80 (2009): 892-900.

45. Vidal, Fábio, Carlos Marcelo S. Figueredo, Ivan Cordovil and Ricardo G. Fischer. "Periodontal Therapy Reduces Plasma Levels of Interleukin-6, C-Reactive Protein, And Fibrinogen in Patients with Severe Periodontitis and Refractory Arterial Hypertension." *J Periodontol* 80 (2009): 786-791.

46. Chung, Shiu-Dong, Ming-Chieh Tsai, Chung-Chien Huang and Chao-Hung Chen. "A Population-Based Study on The Associations Between Chronic Periodontitis and The Risk of Cancer." *Int J Clin Oncol* 21 (2016): 219-223.

47. Dizdar, Omer, Mutlu Hayran, Deniz Can Guven and Tolga Birtan Yılmaz, et al. "Increased Cancer Risk in Patients with Periodontitis." *Curr Med Res Opin* 33 (2017): 2195-2200.

48. Ray, Katrina. "Fusobacterium Nucleatum Found in

Colon Cancer Tissue—Could an Infection Cause Colorectal Cancer?" *Nat Rev Gastroenterol Hepatol* 8 (2011): 662-662.

49. Ahn, Jiyoung, Stephanie Segers and Richard B. Hayes. "Periodontal Disease, Porphyromonas G Ingivalis Serum Antibody Levels and Orodigestive Cancer Mortality." *Carcinogenesis* 33(2012): 1055-1058.

50. Pihlstrom, Bruce L., Bryan S. Michalowicz and Newell W. Johnson. "Periodontal Diseases." *Lancet* 366 (2005): 1809-1820.

51. Schwabe, Robert F. and Christian Jobin. "The Microbiome and Cancer." *Nat Rev Cancer* 13 (2013): 800-812.

52. Demmer, Ryan T., Ludovic Trinquart, Aleksandra Zuk and Benjamin C. Fu, et al. "The Influence of Anti-Infective Periodontal Treatment On C-Reactive Protein: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." *PloS one* 8 (2013): e77441.

53. Algra, Annemijn M. and Peter M. Rothwell. "Effects of Regular Aspirin on Long-Term Cancer Incidence and Metastasis: A Systematic Comparison of Evidence from Observational Studies Versus Randomised Trials." *Lancet Oncol* 13 (2012): 518-527.

54. Flossmann, Enrico and Peter M. Rothwell. "Effect of Aspirin on Long-Term Risk of Colorectal Cancer: Consistent Evidence from Randomised and Observational Studies." *Lancet* 369 (2007): 1603-1613.

55. Baron, John A. and Robert S. Sandler. "Nonsteroidal Anti-Inflammatory Drugs and Cancer Prevention." *Ann Rev Med* 51 (2000): 511-523.

56. Williams, Christopher S., Moss Mann and Raymond N. DuBois. "The Role of Cyclooxygenases in Inflammation, Cancer, And Development." *Oncogene* 18 (1999): 7908-7916.

57. Curtis, Mike A., Patricia I. Diaz and Thomas E. Van Dyke. "The Role of The Microbiota in Periodontal Disease." *Periodontology 2000* 83 (2020): 14-25.

58. Hajishengallis, George and Triantafyllos Chavakis. "Local and Systemic Mechanisms Linking Periodontal Disease and Inflammatory Comorbidities." *Nat Rev Immunol* 21 (2021): 426-440.

59. Louis, Petra, Georgina L. Hold and Harry J. Flint. "The Gut Microbiota, Bacterial Metabolites and Colorectal Cancer." *Nat Rev Microbiol* 12 (2014): 661-672.

60. Helmink, Beth A., MA Wadud Khan, Amanda Hermann, Vancheswaran Gopalakrishnan and Jennifer A. Wargo. "The Microbiome, Cancer, And Cancer Therapy." *Nat Med* 25 (2019): 377-388.

61. Eliot, Melissa N., Dominique S. Michaud, Scott M. Langevin and Michael D. McClean, et al. "Periodontal Disease and Mouthwash Use Are Risk Factors for Head and Neck Squamous Cell Carcinoma." *Cancer Causes & Control* 24 (2013): 1315-1322.

62. Zeng, Xian-Tao, Ling-Yun Xia, Yong-Gang Zhang and Sheng Li, et al. "Periodontal Disease and Incident Lung Cancer Risk: A Meta-Analysis of Cohort Studies." *J Periodontol* 87 (2016): 1158-1164.

63. Maisonneuve, Patrick, Salomon Amar and Albert B. Lowenfels. "Periodontal Disease, Edentulism, And Pancreatic Cancer: A Meta-Analysis." *Ann Oncol* 28 (2017): 985-995.

64. Sun, Jinghua, Min Zhou, Christian R. Salazar, Rosemary Hays, Sukhleen Bedi, Yu Chen, and Yihong Li. "Chronic periodontal disease, periodontal pathogen colonization, and increased risk of precancerous gastric lesions." *Journal of Periodontology* 88 (2017): 1124-1134.

65. Koliarakis, Ioannis, Ippokratis Messaritakis, Taxiarchis Konstantinos Nikolouzakis and George Hamilos, et al. "Oral Bacteria and Intestinal Dysbiosis In Colorectal Cancer." *Int J Mol Sci* 20 (2019): 4146.

66. Gkountouvas, A., M. Nikas, F. Chatjimarkou and D. Thomas, et al. "Thyroid Cancer in Greece. A Tertiary Center Experience." *J BUON* 15 (2010): 674-678.

67. World Health Organization. Oral health surveys: basic methods. Geneva: World Health Organization;1997. https://apps.who.int/iris/bitstream/handle/10665/41905/9241544937

68. Tonetti, Maurizio S., Henry Greenwell and Kenneth S. Kornman. "Staging and Grading of Periodontitis: Framework and Proposal of a New Classification and Case Definition." *J Clin Periodontol* 89 (2018): S159-S172.

69. Machuca, Guillermo, Juan J. Segura-Egea, Gema Jiménez-Beato and Juan R. Lacalle, et al. "Clinical Indicators of Periodontal Disease in Patients with Coronary Heart Disease: A 10 Years Longitudinal Study." *Med Oral Patol Oral Cir Bucal* 17 (2012): e569.

70. Loos, Bruno G., Raymond P. John and Marja L. Laine. "Identification of Genetic Risk Factors for Periodontitis and Possible Mechanisms of Action." *J Clin Periodontol* 32 (2005): 159-179.

71. Haber, Richard S. "Role of Ultrasonography in The Diagnosis and Management of Thyroid Cancer." *Endocrine Practice* 6 (2000): 396-400.

72. Molloy, John, Larry F. Wolff, Angel Lopez-Guzman and James S. Hodges. "The Association of Periodontal Disease Parameters with Systemic Medical Conditions and Tobacco Use." *J Clin Periodontol* 31 (2004): 625-632.

73. Cutress, T. W., J. Ainamo and J. Sardo-Infirri. "The Community Periodontal Index of Treatment Needs (Cpitn) Procedure for Population Groups and Individuals." *Int Dent J* 37 (1987): 222-233.

74. Wiebe, Colin B. and Edward E. Putnins. "The Periodontal Disease Classification System of The American Academy of Periodontology-An Update." *J Can Dent Assoc* 66 (2000): 594-599.

75. Yoon, Hyung-Suk, Wanqing Wen, Jirong Long and Wei Zheng, 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* 127 (2019): 90-95.

76. Löe, Harald. "The Gingival Index, The Plaque Index and The Retention Index Systems." *J Periodontol* 38 (1967): 610-616.

77. Aurilio, Gaetano, Francesco Piva, Matteo Santoni and Alessia Cimadamore, et al. "The Role of Obesity in Renal Cell Carcinoma Patients: Clinical-Pathological Implications." *International journal of molecular sciences* 20 (2019): 5683.

78. Blaizot, Alessandra, Jean-Noël Vergnes, Samer Nuwwareh and Jacques Amar, et al. "Periodontal Diseases and Cardiovascular Events: Meta-Analysis of Observational Studies." *Int Dent J* 59 (2009): 197-209.

79. De Oliveira Ferreira, Railson, Raíra de Brito Silva and Marcela Barauna Magno, et al. "Does Periodontitis Represent A Risk Factor for Rheumatoid Arthritis? A Systematic Review and Meta-Analysis." *Ther Adv Musculoskelet* 11 (2019): 1759720X19858514.

80. Moghadam, Somaye Ansari, Masoomeh Shirzaiy, and Sirus Risbaf. "The associations between periodontitis and respiratory disease." *J Nepal Health Res Counc* 15 (2017):1-6.

81. Helenius-Hietala, Jaana, Anna Liisa Suominen, Hellevi Ruokonen and Matti Knuuttila, et al. "Periodontitis Is Associated with Incident Chronic Liver Disease—A Population-Based Cohort Study." *Liver Int* 39 (2019): 583-591.

82. Al-Maweri, Sadeq Ali, Wael Ibraheem Ibraheem, Mohammad Sultan Al-Ak'hali and Anas Shamala, Esam Halboub, et al. "Association of Periodontitis and Tooth Loss with Liver Cancer: A Systematic Review." *Rev Oncol Hematol* 159 (2021): 103221.

83. Chen, Hui, Shuping Nie, Yuhui Zhu and Ming Lu. "Teeth Loss, Teeth Brushing and Esophageal Carcinoma: A Systematic Review and Meta-Analysis." *Sci Rep* 5 (2015): 15203.

84. Chen, You, Bao-ling Zhu, Cong-cong Wu and Xi Zhang. "Periodontal Disease and Tooth Loss Are Associated with Lung Cancer Risk." *Biomed Res Int* 2020 (2020): 5107696.

85. Hiraki, Akio, Keitaro Matsuo, Takeshi Suzuki and Kazuo Tajima. "Teeth Loss and Risk of Cancer At 14 Common Sites in Japanese." *Cancer Epidem Biomar* 17 (2008): 1222-1227.

86. Lee, Kijeong, Ji Sung Lee, Jinkwon Kim and Huisong Lee, et al. "Oral Health and Gastrointestinal Cancer: A Nationwide Cohort Study." *J Clin Periodontol* 47(2020): 796-808.

87. Momen-Heravi, Fatemeh, Ana Babic, Shelley S. Tworoger and Libin Zhang, et al. "Periodontal Disease, Tooth Loss and Colorectal Cancer Risk: Results from The Nurses' Health Study." *Int J Cancer* 140 (2017): 646-652.

88. Fitzpatrick, Sarah G. and Joseph Katz. "The Association Between Periodontal Disease and Cancer: A Review of The Literature." *J Dent* 38 (2010): 83-95.

89. Hwang, Ing-Ming, Li-Min Sun, Cheng-Li Lin and Chia-Hung Kao. "Periodontal Disease with Treatment Reduces Subsequent Cancer Risks." *QJM* 107 (2014): 805-812.

90. Xu, Li, Guojun Li, Qingyi Wei, Adel K. El-Naggar, and Erich M. Sturgis. "Family History of Cancer and Risk of Sporadic Differentiated Thyroid Carcinoma." *Cancer* 118 (2012): 1228-1235.

91. Mack, Wendy J., Susan Preston-Martin, Luigino Dal Maso and Rosaria Galanti, et al. "A Pooled Analysis of Case–Control Studies of Thyroid Cancer: Cigarette Smoking and Consumption of Alcohol, Coffee, And Tea." *Cancer Causes Controll* 14 (2003): 773-785.

92. Kust, D., J. Staničić and N. Mateša. "Bethesda Thyroid Categories and Family History of Thyroid Disease." *Clin Endocrinol* 88 (2018): 468-472.

93. Nikiforova, Marina N., George C. Tseng, David Steward and Donna Diorio, et al. "MicroRNA Expression Profiling of Thyroid Tumors: Biological Significance and Diagnostic Utility." *J Clin Endocrinol Metab* 93 (2008): 1600-1608.

94. Abdullah, Mardiaty Iryani, Sarni Mat Junit, Khoon Leong Ng and Jaime Jacqueline Jayapalan, et al. "Papillary Thyroid Cancer: Genetic Alterations and Molecular Biomarker Investigations." *Int J Med Sci* 16 (2019): 450.

95. Fallah, Mahdi, Kristina Sundquist and Kari Hemminki. "Risk of Thyroid Cancer in Relatives of Patients with Medullary Thyroid Carcinoma by Age at Diagnosis." *Endocr Relat Cancer* 20 (2013): 717-724.

96. Amundadottir, Laufey T., Sverrir Thorvaldsson, Daniel F. Gudbjartsson and Patrick Sulem, et al. "Cancer as A Complex Phenotype: Pattern of Cancer Distribution Within and Beyond the Nuclear Family." *PLoS medicine* 1 (2004): e65.

97. Hwang, Shin Hye, Eun-Kyung Kim, Hee Jung Moon and Jung Hyun Yoon, et al. "Risk of Thyroid Cancer in Euthyroid Asymptomatic Patients with Thyroid Nodules with An Emphasis on Family History of Thyroid Cancer." *Korean J Radiol* 17 (2016): 255.

98. Lang, Niklaus P., Andreas Joss, Thomas Orsanic and Beatrice E. Siegrist. "Bleeding on Probing. A Predictor for The Progression of Periodontal Disease?" *J Clin Periodontol* 13 (1986): 590-596.

99. Miskiewicz, Andrzej, Grzegorz Szparecki, Marek Durlik and Grażyna Rydzewska, et al. "The Correlation Between Pancreatic Dysfunction Markers and Selected Indices of Periodontitis." *Adv Clin Experim Med* 27 (2018): 313-319.

100. Chen, Sung-Hsiung, Jui-Feng Chen, Yu-Tung Hung and Tzu-Ju Hsu, et al. "Exploring the Relationship Between Periodontitis, Anti-Periodontitis Therapy, And Extra-Oral Cancer Risk: Findings from A Nationwide Population-Based Study." *Biomedicines* 11 (2023): 1949.

101. Kim, Eun Hwa, Sunghyun Nam, Chung Hyun Park and Yitak Kim, et al. "Periodontal Disease and Cancer Risk: A Nationwide Population-Based Cohort Study." *Front Oncol* 12 (2022): 901098.

102. Kang, Eun Joo, Seok-joo Moon, Kyoungmin Lee and Yoon Ji Choi. "Associations Between Missing Teeth and The Risk of Cancer in Korea: A Nationwide Cohort Study." *BMC Oral Health* 23 (2023): 418.

103. Ahn, Hyeong Sik, Hyun Jung Kim and H. Gilbert Welch. "Korea's Thyroid-Cancer "Epidemic"—Screening and Overdiagnosis." *N Engl J Med* 371 (2014): 1765-1767.

104. Hoare, Anilei, Cristopher Soto, Victoria Rojas-Celis and Denisse Bravo. "Chronic Inflammation as A Link Between Periodontitis and Carcinogenesis." *Mediat Inflamm* 2019 (2019):1029857.

105. Landskron, Glauben, Marjorie De la Fuente, Peti Thuwajit and Chanitra Thuwajit, et al. "Chronic Inflammation and Cytokines in The Tumor Microenvironment." *J Immunol Res* 2014 (2014): 149185.

106. Kageyama, Shinya, Toru Takeshita, Kenji Takeuchi and Mikari Asakawa, et al. "Characteristics of The Salivary Microbiota in Patients with Various Digestive Tract Cancers." *Front Microbiol* 10 (2019): 1780.

107. Li, Yuchao, Xuexin Tan, Xida Zhao and Zhongfei Xu, et al. "Composition and Function of Oral Microbiota Between Gingival Squamous Cell Carcinoma and Periodontitis." *Oral Oncol* 107 (2020): 104710.

108. Mitsuhashi, Kei, Katsuhiko Nosho, Yasutaka Sukawa and Yasutaka Matsunaga, et al. "Association of Fusobacterium Species in Pancreatic Cancer Tissues with Molecular Features and Prognosis." *Oncotarget* 6 (2015): 7209.

109. Flanagan, Lorna, Jasmin Schmid, Matthias Ebert and Pavel Soucek, et al. "Fusobacterium Nucleatum Associates with Stages of Colorectal Neoplasia Development, Colorectal Cancer and Disease Outcome." *Eur J Clin Microbiol* 33 (2014): 1381-1390.

110. Zhang, Weiquan, Junwen Luo, Xiaopeng Dong and Shukang Zhao, et al. "Salivary Microbial Dysbiosis Is Associated with Systemic Inflammatory Markers and Predicted Oral Metabolites in Non-Small Cell Lung Cancer Patients." *J Cancer* 10 (2019): 1651.

111. Stasiewicz, Mark, Marek Kwaśniewski and Tomasz M. Karpiński. "Microbial Associations with Pancreatic Cancer: A New Frontier in Biomarkers." *Cancers* 13 (2021): 3784.

112. Zhang, Ling, Yuan Liu, Hua Jun Zheng and Chen Ping Zhang. "The Oral Microbiota May Have Influence on Oral Cancer." *Front Cell Infect Microbiol* 9 (2020): 476.

113. Ma KS, Lai JN, Thota E and Yip HT, et al. "Bidirectional Relation- Ship Between Osteoarthritis and Periodontitis: A Population-Based Cohort Study Over A 15- Year Follow-Up Front". *Immunol* 13 (2022): 909783.

114. Loos, Bruno G. "Systemic Markers of Inflammation in Periodontitis." *J Periodontol* 76 (2005): 2106-2115.

115. Nagy, Ferenc Tamás, Dorottya Gheorghita, Lalli Dharmarajan and Gábor Braunitzer, et al. "Oral Health of Patients Undergoing Percutaneous Coronary Intervention—A Possible Link Between Periodontal Disease and In-Stent Restenosis." *J Pers Med* 13 (2023): 760.

116. Pussinen, Pirkko J., Karolina Tuomisto, Pekka Jousilahti and Aki S. Havulinna, et al. "Endotoxemia, Immune Response to Periodontal Pathogens, And Systemic Inflammation Associate with Incident Cardiovascular Disease Events." *Arterioscler Thromb Vasc Biol* 27 (2007): 1433-1439.

117. Loos, Bruno G., Jeroen Craandijk, Frans J. Hoek and Paulien ME Wertheim-van Dillen, et al. "Elevation of Systemic Markers Related to Cardiovascular Diseases in The Peripheral Blood of Periodontitis Patients." *J Periodontol* 71 (2000): 1528-1534.

118. Memon, Anjum, Imogen Rogers, Priyamvada Paudyal and Josefin Sundin. "Dental X-Rays and The Risk of Thyroid Cancer and Meningioma: A Systematic Review and Meta-Analysis of Current Epidemiological Evidence." *Thyroid* 29 (2019): 1572-1593.

119. Imaeda, Nahomi, Chiho Goto, Yuko Tokudome and Shinkan Tokudome. "Reproducibility of A Short Food Frequency Questionnaire for Japanese General Population." *J Epidemiol* 17 (2007): 100-107.

120. Marshall, James R., Saxon Graham, Brenda P. Haughey and Donald Shedd, et al. "Smoking, Alcohol, Dentition and Diet in The Epidemiology of Oral Cancer." *Eur J Cancer B Oral Oncol* 28 (1992): 9-15.

121. Garrote, L. Fernandez, R. Herrero, R. M. Reyes and S. Vaccarella, et al. "Risk Factors for Cancer of The Oral Cavity and Oro-Pharynx in Cuba." *Br J Cancer* 85 (2001): 46-54.

122. Hujoel, Philippe P., Mark Drangsholt, Charles Spiekerman and Noel S. Weiss. "An Exploration of The Periodontitis–Cancer Association." *Ann Epidemiol* 13 (2003): 312-316.