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Examination of the Association between Periodontal Disease, Tooth Loss, and Risk of Gallbladder Carcinoma : A Case- Control Study in Greek Adults

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Abstract

Objective: To estimate the possible association between periodontal disease (PD) clinical indices, and number of missing teeth and the risk of developing gallbladder carcinoma (GBC) in Greek adults using data from a population based case-control study.

Material and Method: The study sample comprised 80 males and 67 females, aged 45 to 79 years. 49 individuals suffered from GBC- cases and 98 were healthy individuals - controls. All clinical indices examined were obtained via a modified standardized questionnaire and an oral and dental clinical examination. Periodontal status included the following clinical parameters, probing pocket depth (PPD), gingival index (GI), plaque index (PlI), clinical attachment loss (CAL), and bleeding on probing (BOP), and the number of missing teeth. The questionnaire included data regarding the dependent and independent risk factors for GBC development. Univariate and logistic regression models adjusted for possible confounders were carried out for data analysis.

Results: Statistical analysis showed that chronic GB inflammation (p=0.00, OR=2.74, 95% CI=1.28-5.86), smoking (p=0.05, OR=1.63, 95% CI=1.26-2.72), GI (p=0.05, OR=1.56, 95% CI=1.20-2.62), and missing teeth more than four teeth (p=0.03, OR=1.74,95% CI=1.30-3.75, p=0.02, OR= 2.03, 95% CI=1.67-4.11) were statistically significantly associated with the risk of developing GBC.

Conclusions: The current research suggested positive associations of chronic inflammation of the gallbladder, smoking, gingival inflammation, and missing teeth more than four with GBC development.

Keywords: Gallbladder cancer, Periodontal disease, Loss of dentition, Dental disease

Introduction

Primary GBC is the most common biliary tract malignancy and the sixth most common cancer affecting the gastrointestinal tract [1,2]. The majority of cases are diagnosed in advanced stages, resulting in extremely poor prognosis [3]. This late diagnosis may be attributed to the absence of symptoms/clinical signs at initial stages. This leads to lack of early treatment [3]. The prognosis is mainly dependent on histological subtype, grade, and the stage of the tumor at the presentation time. The overall mean survival rate for GBC patients is six months, with a 5-year survival rate of 5% [1]. GBC is a rare malignant tumor in western countries but is much more frequent in some other regions worldwide. The occurrence of GBC is less than 2/100,000 individuals worldwide; however, this has been recorded with extensive variance [4]. Its extensive incidence variation in ethnicity, geography, and cultural differences suggests the possible roles of genetic and environmental

factors associated with its appearance and progression [5,6].

PD, gingivitis and periodontitis, is a multifactorial, and chronic immunological disease [7,8]. Gingivitis concerns the soft tissue surrounding the teeth and is a reversible inflammation. On the contrary, periodontitis is characterized by irreversible loss of periodontal tissue support and leads to tooth loss [9]. Gingivitis may progress to periodontitis in those susceptible individuals with compromised immune system [7,8]. PD global prevalence has been estimated to be 20-50% whereas a rate of 10% of the population globally is affected by severe periodontitis [9-11], and its prevalence varies in different countries [10]. In the United States 42.2% of dentate adults aged 30 years or older suffer from periodontitis, whereas 7.8% suffer from severe periodontitis [12].

GBC appearance has been associated with diverse genetic and environmental factors. To be more specific, main independent etiological factors concern female gender [13], advanced age [13], gallstones family history [14,15], increased BMI [16] and obesity [17], cholelithiasis [13,18], chronic inflammation-cholecystitis and porcelain gallbladder[19], chronic infection by *Salmonella* species, *S. paratyphi* or *S.typhican* [13,20-22], *H. pylori* [23], gallbladder polyp [24], abnormal pancreatobiliary duct junction [25], and high parity (females having had five or more births) [26,27]. Associated risk factors such as Mirizzi's syndrome and bile reflux have also been played an essential role as predisposing GBC factors [28]. Other, dependent etiological factors concern environmental exposure to specific chemicals and heavy metals such as nickel, cadmium, etc. [29], mustard oil [30], argemone oil and butter yellow [31], occupational exposure to benzene [32], free radical oxidation products [33], and smoking [34]. In addition, use of oral contraceptives [27,34], an early age at first pregnancy [26], red chili pepper [35], xanthogranulomatous cholecystitis [36], secondary bile acids [15,37], and genetic factors [38] have also been incriminated in GBC development.

A number of studies have recorded associations between PD, and periodontitis mainly and diverse systemic diseases and disorders, including cancer [39-46]. Especially, prospective studies reported increases in the overall cancer risk associated with PD of 14% to 24%, whereas the association was not attenuated even after adjustment for known risk factors, such as smoking, socio-economic status, and other confounders [44,46,47]. It is possible that the conflicting and controversial associations in specific cancer types could be attributed to differences in study designs, cohort sizes, study populations, 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 based on large samples showed a consistent association between PD and cancer risk, and that risk seemed to increase significantly depending on PD severity [47].

The mechanisms through which cancer may appear among individuals who have PD are not entirely clear. A number of plausible mechanisms have been suggested and inflammation seems to play a significant role in many of those supposed mechanisms. Inflammatory responses are able to produce free radicals and active intermediates (ROS and RNI) causing oxidative/nitrosative stress, that may result in DNA mutations in cells, or they may interfere with DNA repair mechanisms [48]. The inflammatory cells themselves may contribute to the damage by producing ROS and RNI, cytokines, chemokines, and metabolites of arachidonic acid, etc. Those products, in turn, demonstrate a strong affinity for more inflammatory cells, enhancing the vicious cycle [48]. It has also been recorded that periodontal treatment can substantially decrease biomarkers of systemic inflammation [49,50] and that 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, stomach, esophagus, breast, and biliary tract [51,52].

Another possible mechanism is the role of oral microbiota dysbiosis that appears to be involved in the pathogenesis of both periodontitis and systemic diseases, including cancer [53,54]. Previous reports suggested that periodontal tissues or oral mucosa microbiota is implicated in cancer pathogenesis and modify the responses to cancer treatment [55,56]. Oral cavity microbiota is connected to the respiratory tract as is able to enter the respiratory and gastrointestinal tract. Therefore, oral microbiota dysbiosis, mainly in periodontitis, can contribute to carcinogenesis of the gastrointestinal and respiratory tract, such as head-neck squamous cell carcinoma (HNSCC), gastric, lung, pancreatic, and colorectal cancer [57-61]. Ten cancer hallmarks have been described in an effort to explain the complex multistage alterations occurring during cancer pathogenesis and progress [62,63]. The microbiota plays an essential role in the homeostasis of the tumor-micro-environment and modifies almost all cancer hallmarks [64]. Therefore, epidemiologic studies must investigate the role of oral microbiome and/or specific established periodontal pathogens in relation to PD and cancer risk.

No previous prospective or retrospective epidemiological research have been carried out for assessing the possible association between PD and risk of GBC in Greece. The purpose of the current case-control study was to assess the possible association between PD indices and tooth loss and risk of developing GBC in a sample of adults in Greece.

Material and Method

Research design and study population sample

The present survey was based on a case-control design and was carried out between December 2020 and August 2023.

Study size assessment was based on GBC prevalence [65]

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 evaluating periodontal status incidence were used for assessing age group [66]. That procedure led to a study sample of 49 individuals suffering from GBC as case studies and 98 healthy participants as controls. All participants ages ranged from 45 to 79 years. Participants were selected from one dental and two medical private practices and were out-patients of the mentioned practices in the city of Athens.

Cases and controls eligibility Criteria

Inclusion criteria was as follows: Participants should not have been treated by a conservative or a surgical process in their oral cavity in the last 6 months, or prescribed systemic antibiotic regimens, or systematic glucocorticoids, or immune-suppression agents within the previous 6 months. They should also have more than 15 teeth and periodontitis from stage I to IV [67].

Participants that suffered from cardiovascular disease (CVD), diabetes mellitus (DM), rheumatoid arthritis, acute pulmonary diseases or any type of malignancies were excluded from the study protocol as those diseases could potentially affect oral and periodontal tissues [68] and lead to biased secondary associations.

All participants were recruited from 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 [69], age [70], and smoking history [71] are the principal risk factors for periodontitis development as covariates according to epidemiological studies [72].

Advanced GBC patients under medical treatment/metastatic disease, patients with GB metastases of a primary focus at a different location, and hospital patients were excluded from the study. The case group consisted of individuals whose GBC primary diagnosis was based on patients' medical files and CT findings, however the definitive diagnosis was confirmed by percutaneous fine needle aspiration (FNA) or core biopsy, most frequently under ultrasound (US) guidance, and occasionally under CT guidance [73].

The current report was not an experimental one and was not approved by authorized committees (Health Ministry, etc.). All participants were informed about the aims/methods and significance of the present survey and gave their written consent to enroll in the study protocol.

Data collection and intra-oral examination

The interview questionnaire was a modified Medical Questionnaire [74] by Minnesota Dental School. A well-trained and calibrated dental surgeon was responsible for completing the questionnaire and the intra-oral examination. The collected data included the medical/dental history of the participants, and epidemiological variables, such as age, gender, smoking status, educational and socio-economic status, etc. Participants' age was classified as 45-50, 51-60, 61-70,71+, 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 (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 intra-examiner variance was assessed by a sample of 30 (20%) individuals that was chosen randomly and re-examined clinically by the same dentist after three weeks, and no significant differences were recorded between the 1st and the 2nd clinical examination *(Cohen's Kappa = 0.95*). During the mentioned time period no oral hygiene instructions were given to the participants.

The mentioned dental surgeon completed all 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. Third molars and remaining roots were excluded from scoring.

The oral and dental examination focused on periodontal health condition and included assessment of PPD, CAL, PlI, GI, and BOP as a measure of PD status. All PD indices were assessed at four sites per tooth (mesio-lingual, mesio-buccal, disto-lingual, and disto-buccal) in all four quadrants and the worst values of the indices recorded to the nearest 1.0 mm and coded as dichotomous variables.

PPD was classified as 0-3.00 mm (absence of disease/mild disease) and ≥ 4.0 mm (moderate and severe disease) for mean PPD [75], CAL severity was classified as mild, 1-2.0 mm of attachment loss and moderate/severe, ≥ 3.0 mm of attachment loss [76], and the number of missing teeth as none, 1-4, 5-10, >10 missing teeth [77]. Gingival inflammation was determined by the examination of four sites per tooth, and its severity was coded as follows:-score 0: healthy gingival tissue and/or mild gingival inflammation, that corresponds to Löe and Silness [78] 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.

PlI, by Löe and Silness [79] was assessed by the same probe at the mentioned sites. The presence of dental plaque was determined whether it was visualized with naked eye or existed in abundance of soft matter within the gingival pocket and/or

on the tooth and gingival margin (score 2 and 3, respectively, according to PII) and considered as present if at least one site showed the characteristic sign.The presence/absence of BOP were recorded and coded as dichotomous variables.

Body Mass Index (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 GBC development [80].

Statistical analysis

The univariate analysis model was carried out to assess the association between the independent indices examined and the GBC risk, separately. Categorical data were shown as frequencies and percentages. Cohort-related variables, including socio-demographic factors (age, income, education), comorbidities (GBC family history, increased BMI, chronic GB inflammation), self-reported questionnaire (smoking status, exposure to environmental pollutants, etc.), were analyzed using the univariate model. Multivariate logistic regression analysis was carried out to assess the associations between the dependent variable, GBC, and independent ones using the Enter method, whereas the Stepwise method was applied to assess the significant associations among the variables examined. Unadjusted and Adjusted Odds Ratios (OR's) and 95% (Confidence Interval) CI were also recorded.

Statistical analysis was performed by 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 sample was 59.6 ± 3.4 years. The univariate analysis is presented in **Table 1** regarding the examined variables. Previous GB chronic inflammation (p=0.01) and dental plaque accumulation (PII) (p=0.00) were found to be statistically significantly associated with the risk of developing GBC. **Table 1** also presents the unadjusted OR's and 95% CIs. According to the step 1[a] of the logistic regression model, the main findings were that previous GB chronic inflammation (p= 0.04), smoking (p= 0.05), and missing teeth more than four (p= 0.04, OR= 1.62,95% CI=1.19-3.36, p= 0.03, OR= 1,81, 95% CI= 1,31-3,95) were statistically significantly associated with the risk for GBC development.

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	22 (44.9)	58 (59.2)	0.10	0.56 (0.28-1.12)
Females	27 (55.1)	40 (40.8)		
Age (years)				
45-49	8 (16.3)	21 (21.4)		
50-59	12 (24.5)	30 (30.6)	0.65	_____
60-69	21 (42.9)	34 (34.7)		
70+	8 (16.3)	13 (13.3)		
Socio-economic status				
Low	27 (55.1)	44 (44.9)	0.24	1.51 (0.76-3.00)
High	22 (44.9)	54 (55.1)		
Education level				
Low	21 (42.9)	40 (40.8)	0.81	1.09 (0.54-2.18)
High	28 (57.1)	58 (59.2)		
Previous GB chronic inflammation				
Absence	19 (38.8)	59 (60.2)	**0.01***	0.42 (0.21-0.84)
Presence	30 (61.2)	39 (39.8)		
Body Mass Index				
<30 kg/m^2	18 (36.7)	52 (53.1)	0.06	1.95 (0.96-3.93)
≥ 30 kg/m^2	31 (63.3)	46 (46.9)		
GB family history				
Absence	20 (40.8)	44 (44.9)	0.64	1.18 (0.59-2.37)
Presence	29 (59.2)	54 (55.1)		

Smoking Never Previous/Current	 22 (44.9) 27 (55.1)	 51 (52.0) 47 (48.0)	0.41	0.75 (0.38-1.50)
Occupational exposure (Mustard Oil, argemon oil) Yes (Butter yellow, heavy metals) No	 12 (24.5) 37 (75.5)	 19 (19.4) 79 (80.6)	0.48	1.35 (0.59-3.07)
Probing pocket depth 0-3.00 mm ≥ 4.0 mm	 20 (40.8) 29 (59.2)	 50 (51.0) 48 (49.0)	0.24	0.66 (0.33-1.33)
Clinical Attachment Loss Absence/Mild: 1.00-2.00 mm Moderate/Severe: ≥ 3.0 mm	18 (36.7) 31 (63.3)	47 (48.0) 51 (52.0)	0.20	0.63 (0.31-1.27)
Gingival Index Absence/Mild Inflammation Moderate/Severe Inflammation	16 (32.7) 33 (67.3)	46 (46.9) 52 (53.1)	0.10	0.55 (0.27-1.12)
Plaque Index Absence Presence	12 (24.5) 37 (75.5)	48 (49.0) 50 (51.0)	0.00*	0.34 (0.16-0.72)
Bleeding on probing Absence Presence	20 (40.8) 29 (59.2)	45 (45.9) 53 (54.1)	0.56	1.23 (0.62-2.47)
Tooth Loss None 1-4 Teeth 5-10 Teeth >10 Teeth	 5 (10.2) 7 (14.3) 22 (44.9) 15 (30.6)	 8 (8.22) 21 (21.4) 42 (42.8) 27 (27.6)	0.76	_____
* p-value : statistically significant				

Table 2 also presents adjusted ORs with 95% CIs and the final step 12[a] in which previous GB chronic inflammation (p=0.00), smoking (p= 0.05), gingival inflammation (p=0.05) and missing teeth more than four (p=0.03, OR=1.74,95% CI=1.30-3.75, p= 0.02, OR=2,03, 95% CI=1,67-4,11) were statistically significantly associated with the risk of developing GBC after adjusting for known confounders, smoking and socioeconomic status.

Discussion

PD as a chronic infectious disease has been associated with diverse systemic diseases and disorders [81-84]. Epidemiological studies have suggested an association between periodontitis, tooth loss and the risk of cancers in diverse organs such as head and neck region, upper gastrointestinal system, pancreas, lungs, etc. [58,59,85-96]. However, those associations have little practical significance as prevention indices [85], even though useful aspects have been provided on the role of PD treatment in decreasing the risk of different types of cancers [97].

The outcomes of the current research showed that GB chronic inflammation, smoking, gingival inflammation, and missing teeth more than four were statistically significantly associated with the risk for developing GBC.

GBC appearance, as already mentioned, has been associated with diverse genetic and environmental factors.

Gender is a known cancer risk factor; however it is considered as a confounder. The results revealed no association between gender and GBC risk, finding that was not in accordance with those from previous reports [13,98]. It is also known that older individuals are in a higher risk for total cancer [13,99], PD initiation and progression [100], however age is also considered as a confounder. No association was recorded between age and GBC risk in the current study.

Other crucial confounders are socio-economic status and educational level; however, it has been proven that their possible role in other types of cancer. Socioeconomic patterns in all-cancer, and cancer mortality have been changed dramatically over time. Individuals with lower education and income status showed higher mortality and incidence rates than the more well-off ones, with a high risk being particularly significant for gastric, lung, cervical, liver, and colorectal cancer

Table 2. Presentation of association between potentially risk factors and GBC according to Enter (first step-1[a]) and Wald (last step 12[a]) 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	,351	,432	,662	1	,42	,70	,30	1,64
	age.groups	,112	,221	,079	1	,79	1,12	,49	2,15
	socio.econ.st	-,456	,425	1,154	1	,28	,63	,27	1,46
	educ.level	-,401	,429	,875	1	,35	,67	,29	1,55
	chron.inflamm	,853	,423	4,072	1	**,04***	2,35	1,03	5,37
	body.mass.ind	,270	,447	,364	1	,55	1,31	,55	3,15
	family.history	,168	,498	,135	1	,71	,85	,35	2,07
	smok.status	,634	,417	3,279	1	**,05***	1,40	1,21	2,53
	occup.expos	,580	,423	1,874	1	,17	1,80	,78	4,09
	clin.att.loss	,299	,417	,513	1	,47	1,35	,60	3,05
	prob.pock.depth	,222	,446	,248	1	,62	1,25	,52	2,99
	plaque. index	,288	,552	,272	1	,60	,75	,25	2,21
	gingival.index	1,302	,548	3,141	1	,07	1,22	1,11	2,57
	bleed.on.prob	,105	,553	,036	1	,850	1,11	,38	3,28
	tooth.loss (none)			3,581	3	**,06***			
	tooth loss (1-4)	-,435	,298	4,882	1	**,05***	1,53	1,17	2,78
	tooth loss (5-10)	,502	,221	5,112	1	**,04***	1,62	1,19	3,36
	tooth loss (>10)	,544	,244	5,448	1	**,03***	1,81	1,31	3,95
	Constant	3,454	1,087	10,109	1	,00	,03		
Step 12[a]	smok.status	,655	,502	3,502	1	**,05***	1,63	1,26	2,72
	chron.inflamm	1,237	,388	6,743	1	**,00***	2,74	1,28	5,86
	gingival.index	1,271	,426	4,891	1	**,05***	1,57	1,20	2,62
	tooth.loss (none)			4,992	3	**,04***			
	tooth.loss (1-4)	-,481	,309	5,109	1	**,03***	1,68	1,27	3,02
	tooth.loss (5-10)	,513	,257	5,330	1	**,03***	1,74	1,30	3,75
	tooth.loss (>10)	,581	,258	5,731	1	**,02***	2,03	1,67	4,11
	Constant	3,732	,839	19,807	1	,00	,024		

a. Variable(s) entered on step 1: gender, age.groups, socio.econ.st, educ.level, chron.infect, body.mass.ind, family.history, smok.status, occup. expos, clin.att.loss, prob.pock.depth, ging.index, plaque.index, bleed.on.prob, tooth.loss.

[101]. In the present research no associations were recorded between those variables and GBC risk.

GBC family history was not found to be significantly associated with the GBC risk, finding that was not in accordance with those from previous reports [102,103].

Obesity and increased BMI have been linked with many types of cancer including breast, colorectal, prostate, GBC, etc. [16,17,104]. The present research did not confirm such an association.

Chronic inflammation-cholecystitis and porcelain gallbladder is an essential independent etiological factor for GBC development [26], finding that was in accordance with the current study.

Smoking is a causal risk factor of total cancer [105]. Several carcinogenic compounds in tobacco such as polycyclic aromatic hydrocarbons (PAH), arylamines and nitrosamines, are factors responsible for carcinogenesis. In addition, exposure to tobacco smoke has been linked with mutational or epigenetic alterations in cellular signaling pathways, which are involved in GBC pathogenesis [34]. The current study confirmed its role as a causal risk factor.

Other dependent etiological factors concern environmental exposure to specific chemicals and heavy metals [29-33]. No associations were found in the current survey between those etiological factors and the risk for GBC development.

Among the PD indices examined, GI was found to be statistically significantly associated with the risk for GBC development. GI expresses the gingival inflammation severity, however that index is not frequently used in epidemiological studies despite the fact that assesses the gingival tissue inflammatory load. Previous reports suggested a special role for gingival inflammation as a risk factor for diverse types of cancer [106,107], whereas similar studies recorded no associations [108-110].

PPD assesses PD severity [111], and the outcomes showed that was not statistically significantly associated with the risk for GBC development. In the literature, only one study has investigated the examined association, and revealed a significantly greater risk of GBC diagnosis among individuals who self-reported a history of PD compared with those with no PD history (HR=1.73, 95% CI=1.01-2.95). However, in never-smokers, the association was significantly reduced (HR= 1.26, 95% CI= 0.59-2.68) [44].

CAL is a crucial index of cumulative tissue destruction, including previous PD, whereas PPD is an indicator of current disease status inflammation [112]. The outcomes showed no association between CAL and the risk for GBC development. Previous studies recorded associations between CAL and other types of cancers [113,114]. PPD and CAL concern the chronic inflammation long-term stages including destructive processes signs of a chronic inflammatory response [115].

BOP is an essential index of periodontal examination and diagnosis, and the most valid PD activity indicator [116]. It expresses the host's vascular response in relation to hyperemia, the capillaries' dilation and enhanced blood flow in the inflammation region, and it is a widely used criterion to diagnose gingival inflammation [116]. No statistically significantly association was observed concerning BOP between cases and controls, finding that was in accordance with a similar previous research [114].

PII assesses dental plaque accumulation. In a previous study it was found that poor oral hygiene, as reflected in the amount of dental plaque, was associated with increased cancer mortality, as based on the findings, the high bacterial load on tooth surfaces and in gingival pockets over a prolonged time could play a role in carcinogenesis [117]. No association between PII and risk for GBC was recorded in the current study. Similar results were observed in previous reports [118,119], whereas Zhang et al. [120] suggested that poor oral health was associated with higher risks of total cancer incidence and diverse site-specific cancers except for GBC.

Tooth loss is the final result of advanced periodontitis. A number of prospective reports have recorded an association between the number of missing teeth and the risk of cancer in various locations [42,110,121]. Similarly, case-control studies have revealed strong associations for tooth loss and oral [122,123], esophageal [124], upper gastro-intestinal [125], gastric [126], pancreatic [127] and lung [41,106,122] cancers.

The mechanisms that are responsible for cancer development among PD patients are not entirely clear. A number of plausible mechanisms have been suggested and inflammation appears to play a significant role in many of those. Moreover, inflammation is a crucial cancer hallmark as is necessary for malignant transformation [62].

PD is a prototype inflammation process that induces chronic low-grade inflammation if left untreated, and a persistent low-grade inflammation has been associated with cancer [127-130]. Persistent chronic periodontitis leads to alterations in the mononuclear cell-cytokine system resulting in a much stronger inflammatory response than common exposure to bacterial stimuli such as lipopolysaccharide (LPS) [130,131]. Genetic polymorphisms of inflammatory cytokines may contribute to susceptibility to [128] carcinogenesis. Chronic periodontitis patients have an inherent defect in their immune system, particularly in relation to bacterial clearance and tumor immune surveillance [132], that may increase their susceptibility to cancer.

On the other hand, GBC is a critical model for understanding inflammation-associated carcinogenesis, since gallstones can

result in GB inflammation [133]. Another suggested GBC risk factor, infection caused by *Salmonella enterica* serovariant Typhi, has also an inflammatory component [134], as circulating inflammatory biomarkers, cytokines and chemokines have been associated with GBC development [135-138], however that association requires further investigation [138].

The human flora appears to play an essential role in normal physiological functions [139], and in carcinogenesis [140]. In the normal oral cavity, more than 700 types of bacteria live, among which red complex is responsible for PD [141]. The red complex consists of *P. gingivalis*, *T. forsythia*, and *T. denticola* [141]. Those Gram-negative anaerobic bacteria are able to release virulence factors to interfere in the host's defense system and destroy periodontal tissue and host's immune system [141]. The subgingival biofilms in periodontitis act as gram-negative anaerobic bacteria reservoirs of *P. gingivalis* and *A. actinomycetemcomitans* [142], that release enzymes and invade to gingival epithelial cells [143]. Those enzymes and other bacterial components such as endotoxins, and metabolic by-products that are toxic to tissues, may cause direct damage to DNA of the surrounding epithelial cells, or are able to induce mutations in proto-oncogenes and tumor suppressor genes, or interfere with the molecular signaling pathways involved in cell survival and/or proliferation [144]. *P. gingivalis*is a periopathogenic bacterium that mediates the local inflammatory response of periodontitis [145], interferes with physiological metabolism, invades gingival epithelial cells, and inhibits apoptosis [146], that is a cancer hallmark [147]. Previous reports have recorded an association between *P. gingivalis* and digestive tract cancer [148,149].

A large amount of gram-negative anaerobic bacteria in individuals with periodontitis has been revealed in the periodontal pockets [149] and may become detached and be micro-aspirated or ingested. Although the release into the blood circulation of those oral bacteria is not permanent, periodontal pathogens such as *P. gingivalis* can evade their destruction by phagocytes via protease release [150]. The bacterium can further evade their destruction by regulating Th2-cell-mediated, anti-inflammatory responses to favor M2 macrophage phenotype production, that are less capable of destroying them [151]. Dendritic cells cannot destroy *P. gingivalis*, therefore allowing those to reach distant organs [152]. It is evident that *P. gingivalis* could survive within the systemic blood circulation and remain viable enough to reach remote regions and cause deleterious effects. That theory has been supported by the observation that periodontal pathogens have been revealed in many body locations except the oral cavity such as blood vessels, atheromatous plaques [153], lung aspirates [154], lymph nodes [155], pericardial fluid [156], liver [157], tonsils [158], spinal infections [159] and the appendix [160]. Periodontal pathogens have also been detected in gastric precancerous lesions [161], in colorectal adenomas [162] and certain cancers such as colorectal [162,163], oral [164], esophageal, and gastric cancers [165,166].

Periodontitis has been linked to a number of immune-inflammatory diseases, some of which are independently associated with increased risk of malignancies [167]. Pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, IL-13 and TNF-α, are up-regulated in periodontitis, stimulate cellular proliferation, remodel the extracellular matrix, and activate immune cells [168]. The protumorigenic function of TNF-α and IL-6 mediated through the transcription nuclear factor NF-κB leading to stimulation of cell proliferation and survival . NF-κB also controls the expression of many genes associated with inflammation and therefore is involved in a feed-forward loop by driving inflammation that results in further NF-κB activation. It is a critical mediator in any chronic inflammation, including periodontitis, and carcinogenesis [169].

PD is also often accompanied by increasing levels of inflammatory biomarkers in blood circulation, as already mentioned [170], such as Il-6, TNF-α, and prostaglandin E2 (PGE2), in response to periodontal inflammation and are responsible for systemic effects at remote body locations [171]. The local immune mediators activated as a consequence of periodontal infection, in blood circulation, may lead to the production of large amounts of acute-phase proteins such as serum C-reactive protein (C-rp), a systemic inflammation biomarker and other systemic inflammatory mediators, such as histamine and serotonin, bradykinin, eicosanoids such as thromboxanes, leukotrienes, and PGs [171]. Increased levels of C-rp have been associated with PD [171-174], and periodontal pathogens [173-176], whereas increased serum C-rp levels have been also associated with increased risk of precursor lesions [177] and diverse types of cancers [178,179]. In addition, pathogenic bacteria can enter the blood circulation [180], and they are associated with diverse systemic diseases, disorders and cancers [181]. In the blood circulation periodontal bacteria may cause damage via their LPS component, by inducing either a systemic [182] or a local inflammatory response at the site where they colonize.

Reactive oxygen species (ROS) and reactive nitrogen species (RNI) are free radicals, produced by normal cellular metabolism, and act as a protective mechanism against bacterial pathogens by direct effects and through recruitment of innate immune response cells [183]. In high concentration, free radicals induce tissue destruction through DNA damage and lipid and protein peroxidation [184]. Abnormal host responses to the microbial infection observed in periodontitis lead to excess ROS and RNI production in periodontal tissues [184], and this is partly mediated by pro-inflammatory cytokines. As free radical concentration increases in the periodontal tissues, ROS and RNI diffuse into the blood circulation, leading to increased oxidative and nitrosative stress and eventually distant tissue/organ damage [184]. ROS and RNI production results in a signaling cascade that triggers the pro-inflammatory cytokines and chemokines production thereby up-regulating

systemic inflammation [185]. Oxidative stress from other inflammation causes, including smoking, toxins, diabetes, and obesity, also impact on the periodontitis progression. Free radicals contribute to carcinogenesis by the up-regulation of systemic inflammation or by direct DNA damage, which can lead to events associated with carcinogenesis such as genomic instability, transcriptional arrest, and replication errors. Eventually, ROS at very low and impermanent levels seem to increase cell proliferation, survival and migration and may therefore impact on tumor progression [186].

Epigenetic alterations leading to hypermethylation of E-cadherin and cyclooxygenase-2 have been associated with chronic periodontitis and may be associated with increased cancer risk [187]. Epigenetic mechanisms are implicated in normal development; however, epigenetic process disruption has been observed to play a crucial role in oncogenesis. Epigenetic alterations in cancer concern DNA methylation, histone modifications, non-coding RNAs, and nucleosome positioning [188]. Epigenetics has not been extensively investigated in periodontitis, however, there is some evidence that epigenetic alterations play a role in the development of periodontitis [189]. An increase in E-cadherin and cyclooxygenase-2 gene hypermethylation is implicated in tumor growth and metastasis [190]. Similarly, it has been found that *P. gingivalis* can induce DNA methylation in normal gingival epithelial cells, finding confirmed in mice infected with *P. gingivalis* and in human periodontal tissues obtained from individuals with periodontitis [191]. Periodontal bacteria involved in metabolic processes, produce several chemical products that can influence tumorigenesis and tumor progression. Nitrosamines have been involved in the development of human cancers for over 40 years and this is considered to be mediated through direct damage to DNA [192]. Nitrosamines dietary sources such as preserved and cured aliments have been involved in nasopharyngeal, esophageal, gastric, pancreatic and colorectal cancers although the data supporting that association remains inconclusive and controversial [193].

Acetaldehyde is the main oxidation product of ethanol. *In vitro* and *in vivo* studies have shown that has mutagenic and carcinogenic effects through genetic events, such as inducing point mutations and chromosomal aberrations and interfering with DNA repair. Those effects are mediated directly by covalent binding to DNA and indirectly through folate catabolisation, with reduced folate levels resulting in DNA hypomethylation, an event that has been observed in many human cancers [194]. It has been suggested that acetaldehyde is a local carcinogen in humans, and oral bacteria such as *Neisseria*, *Streptococcus* and *Prevotella*species are capable of metabolizing ethanol to acetaldehyde [195].

Some interfering factors should be taken into account in interpretation of the observed outcomes regarding the relation between PD and cancer, in general. Those studies have used different criteria in the definition and measurement of PD. Some used the common PD indices, such as PPD, GI, CAL, tooth loss and others based on patient history, self-questionnaires, clinical, and radiographic findings as criteria for PD patients [196]. 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 [123].

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 [197]. Those variables are age, gender, genetic, educational, and socioeconomic status as are considered as risk factors for both diseases. Actually, research studies which are adjusted for those variables can be used for the estimation of PD as an independent risk factor of cancer [90].

Conclusions

In conclusion, smokers and individuals with chronic GB inflammation, gingival inflammation and with missing teeth more than four were at significantly higher risk for GBC development. Those associations remained after controlling for certain confounders such as smoking status and SES.

Conflict of Interest

The authors declare that they have no conflict of interests.

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