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Risk of Grade II Oligodendroglioma for Individuals with Periodontal Disease and Tooth Loss Versus Healthy Individuals: A Case – Control Study in Greece

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Abstract

Background: Previous studies have demonstrated associations between Periodontal Disease and various malignancies, including oral/head and neck, esophageal, gastric, lung, kidney, and prostate cancers, as well as hematological malignancies.

Objective: This investigation aimed to evaluate the potential association between Periodontal Disease and the risk of developing Oligodendroglioma (grade II).

Methods: The study sample comprised 42 individuals diagnosed with oligodendroglioma (grade II) and 126 matched healthy controls, recruited from one dental and three medical private practices. Participants completed a standardized health questionnaire and underwent clinical periodontal examination. Periodontal status was evaluated using Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), and number of missing teeth.

Data were analyzed using univariate and multivariate logistic regression models, adjusting for potential confounding factors.

Results: Younger age (p=0.076, OR=0.819, 95% CI= 0.528-1.332) and the presence of deep periodontal pockets (p=0.089, OR= .786, 95% CI= 0.458-2.727) were positively associated, though not necessarily to a statistically significant degree, with the risk of developing Oligodendroglioma (grade II),whereas a positive family history of the disease (p=0.000, OR=3.479, 95% CI=2.103-6.022) demonstrated a statistically significant positive association.

Conclusion: This study suggests that younger age of individuals and deep periodontal pockets were positively, though non-significantly, associated with grade II Oligodendroglioma risk, whereas a positive family history of the disease exhibited a statistically significant positive association.

Keywords: Periodontal Disease; Oligodendroglioma (Grade II); Risk Factors; Adults

Introduction

Gliomas constitute the most prevalent primary solid malignancies of the Central Nervous System (CNS) [1] and are stratified into four distinct grades based on histological and molecular criteria, according to the 2021 World Health Organization (WHO) CNS classification [2]. Within this framework, CNS WHO grade 2 Low-Grade Gliomas (LGGs) encompass Oligodendrogliomas (OGs) and Astrocytomas (ACs), predominantly affecting young adults during their third and fourth decades of life. Characterized as a rare subtype of diffuse neuroepithelial tumors originating within the CNS, OGs represent the third most common primary brain tumor, following glioblastoma and diffuse AC, accounting for approximately 5% of all primary CNS neoplasms [3]. In the United States, the annual incidence is estimated at approximately 1,000 new cases. These tumors are stratified into two distinct clinical categories: grade II OGs and grade III (anaplastic) OGs. While predominantly diagnosed in individuals aged 25 to 45 years, grade III malignant counterparts typically manifest a decade later than grade II tumors, with infrequent occurrences in pediatric or geriatric populations.

Notably, LGGs retain the potential for malignant transformation into more aggressive High-Grade Gliomas (HGGs), and it is hypothesized that anaplastic OG can progress from a lower-grade precursor through the sequential acquisition of specific genetic alterations [4].

Consistent with oncogenic processes in other malignancies, oligodendrogliomas originate from distinct molecular alterations, including genetic mutations that possess critical diagnostic and prognostic utility as essential biomarkers for tumor characterization and classification [5]. Genetically, OG is defined by the definitive presence of either an *IDH1* or *IDH2* mutation [6], co-segregating with the co-deletion of chromosome arms 1p and 19q [2, 7, 8]. Despite substantial advancements in molecular biology, the precise biological mechanisms and signaling pathways driving oligodendrogliogenesis remain partially elucidated. Histologically, these tumors are characterized by sheets of isomorphic round nuclei surrounded by a clear cytoplasmic halo, giving rise to the pathognomonic "fried-egg" appearance. Grade III OGs harbor a worse prognosis compared to grade II neoplasms due to the presence of anaplastic features, including marked nuclear atypia, focal necrosis, microvascular proliferation, hypercellularity, and elevated mitotic activity. However, a definitive histopathological distinction between the two grades remains challenging in certain clinical contexts [5].

Conventional and emerging treatments include safe surgical resection followed by adjuvant radiotherapy [9]. For recurrent cases, salvage options comprise reoperation and chemotherapy; nevertheless, therapeutic efficacy remains limited, often yielding suboptimal clinical outcomes [10].

While the precise etiology remains poorly understood, high-dose ionizing radiation to the head and neck region, typically administered for preceding malignancies, is a well-established environmental trigger accelerating glioma pathogenesis, potentially including oligodendroglial lineages. Factors previously found to be associated with the larger category of glioma, which includes oligodendroglial tumors [11], such as ionizing radiation, family history of brain tumors, and allergic disease, may also be specifically associated with oligodendroglial tumors [12].

Individuals with a familial predisposition to central nervous system malignancies exhibit an elevated risk. Specifically, a positive family history of brain tumors is significantly associated with an increased risk of developing anaplastic OG (OR=2.2; 95% CI: 1.1-4.5). Neoplastic onset is most prevalent in young to middle-aged adults, peaking predominantly during the third and fourth decades of life, with a documented male-to-female predominance of approximately 2:1 [12].

Interestingly, a history of atopic diseases demonstrates an inverse, protective relationship with oligodendroglial tumorigenesis. An history of asthma only is strongly associated with a reduced risk of both low-grade OG and anaplastic variants [13]. In addition, previous exposure to varicella-zoster virus (chicken pox) has similarly been pooled with a decreased risk of developing oligodendroglial tumors [14].

Periodontal Disease (PD), particularly in its severe form of periodontitis, is a chronic inflammatory condition affecting the supporting structures of the dentition, primarily initiated by bacterial infection of the gingival tissues and the surrounding alveolar bone [15]. As a sustained host inflammatory response to pathogenic dental plaque biofilm [16], PD contributes to systemic inflammation, characterized by elevated circulating levels of pro-inflammatory biomarkers, including interleukin-6 (IL-6) and C-Reactive Protein (CRP) [17]. According to the Global Burden of Disease (GBD) Study 2019, severe periodontitis affected approximately 1.1 billion individuals worldwide, representing a substantial increase since 1990 [18]. Beyond oral pathology, PD is epidemiologically and pathophysiologically linked to various systemic comorbidities, including Cardiovascular Diseases (CVDs) [19], Diabetes Mellitus (DM) [20], rheumatoid arthritis [21], and several malignancies [22-26], potentially driven by shared risk factors and common inflammatory pathways [20, 23, 26, 27]. Over the past few decades, growing evidence suggested that PD may elevate overall cancer incidence as well as specific site-related malignancies [27, 28].

Accumulating evidence further indicates a potential pathophysiological link between PD and the pathogenesis or exacerbation of CNS disorders. Notably, Porphyromonas gingivalis has been isolated from post-mortem brain tissues of patients diagnosed with various neurological conditions, including Alzheimer's Disease (AD) and intracranial aneurysms. Concurrently, periodontitis constitutes a statistically significant risk factor for accelerated amyloid-β peptide deposition [28], cognitive decline [29], and the clinical onset of AD [30]. Lipopolysaccharide (LPS) derived from *P. gingivalis* serves as a standard experimental model to elucidate the systemic impact of PD on oncological progression [31-35] and CNS pathologies [36-38], with immunofluorescence labeling definitively demonstrating the localization of *P. gingivalis* LPS within cerebral tissues [39].

To date, a limited number of studies have specifically investigated PD as a potential risk factor for brain malignancies [40-42], yielding inconsistent findings. For instance, a prospective cohort study examining malignancies rarely reported in association with PD yielded largely negative results regarding brain cancer [HR: 0.99, 95% CI: 0.61-1.59] [40]. Conversely, alternative evidence showed that poor periodontal status [Probing Depth (PD)≥6.0 mm and Attachment Loss (AL)>5.0 mm] was present in 42.9% (9/21) of patients with glioma, a prevalence significantly higher than that observed in patients with benign tumors [41]. Moreover, a recent case-control study reported that oral microbiota composition and gene functions are significantly associated with human brain glioma grade [42].

Despite these prior investigations, the reported associations between PD and cancer risk remain inconsistent, even after adjusting for potential confounding factors such as smoking, educational attainment, and Socioeconomic Status (SES). The underlying biological mechanisms remain partially elucidated; however, proposed pathways suggest that PD influences neuro-oncogenesis through systemic inflammatory responses mediated by circulating pro-inflammatory factors, direct hematogenous translocation of oral pathogens, and modulation of host immune surveillance [43, 44].

Epidemiological data regarding the potential association between PD severity and OG susceptibility within the Greek population remain non-existent. Consequently, this case-control study constitutes the first nation-specific investigation designed to evaluate the relationship between clinical periodontal indices and number of missing teeth and the risk of Grade II OG development in a cohort of Greek adults.

Materials and Methods

Study design and sample size estimation

This case-control study enrolled 168 participants, 91 males and 77 females, and age range 35 to 65 years, comprising 42 patients diagnosed with OG (grade II) and 126 matched healthy controls. Sample size estimation was performed using the EPI-TOOLS platform (ausvet.com.au) [45], assuming a 95% confidence level, 80% statistical power, and based on established OG prevalence. Individuals' recruitment was conducted across three medical clinics and one private dental practice between June 2023 and April 2026. All participants underwent a comprehensive clinical oral examination and completed a structured, standardized medical and dental history questionnaire [46].

Periodontal status was evaluated in accordance with the WHO age-specific guidelines [47]. To mitigate selection and recall biases, controls were individually matched to cases based on age and gender, both recognized risk factors for periodontitis and critical confounding variables in multivariable analyses [48, 49].

Eligibility criteria

Inclusion criteria for both cohorts required participants to have more than 15 natural teeth, a diagnosis of periodontitis ranging from stage I to IV [50], and to be from comparable SES and educational backgrounds within the same urban area. To minimize genetic confounding, individuals from the same family were excluded.

Conversely, exclusion criteria comprised, receipt of any surgical or non-surgical periodontal therapy within the preceding six months, administration of systemic glucocorticoids, immunosuppressive agents, or systemic antibiotics during the same six-month time period, presence of systemic comorbidities known to influence periodontal status, including DM, CVDs, acute pulmonary conditions, such as, chronic obstructive pulmonary disease, or concurrent malignancies [46], and a diagnosis of grade III OG, owing to its distinct adverse clinical course and poor prognosis.

Clinical assessment and diagnostic procedures

MRI with and without gadolinium contrast serves as the primary modality for provisional identification of the tumor. CT scans are concurrently utilized to detect tumor calcification, a hallmark radiographic feature observed in up to 90% of oligodendroglial tumors. However, definitive diagnosis cannot be established via imaging alone and mandates histopathological evaluation of tissue specimens obtained via surgical resection or stereotactic biopsy. Classic light microscopy reveals a monotonous sheet of isomorphic cells with round nuclei and a clear cytoplasmic halo, widely known as the "fried-egg" artifact. According to the current WHO Classification of Tumors of the Central Nervous System, a definitive diagnosis of OG strictly requires the demonstration of specific molecular markers such as, IDH Mutation Status, detection of a mutation in either the *IDH1* (typically R132H) or *IDH2* gene, and 1p/19q co-deletion, complete, concurrent loss of chromosome arms 1p and 19q, usually evaluated *via* Fluorescence *In Situ* Hybridization (FISH) or Next-Generation Sequencing (NGS). In case a tumor appears histologically as an OG but lacks this co-deletion, it is molecularly reclassified as an astrocytoma [2, 51]. The study excluded individuals who underwent any form of treatment, such as surgery, radiotherapy, chemotherapy (target therapies or IDH inhibitors etc.) [51, 52], immediately following the diagnosis of the disease, as this could have affected their periodontal status and the intra-examiner variance.

Data collection and confounder assessment

Prior to the clinical examination, all participants completed a standardized, modified medical questionnaire [46]. Due to the relatively small case sample size, SES, educational attainment, and smoking history were omitted from the multivariable models to prevent multicollinearity and over-fitting. Consequently, statistical adjustment for residual confounding was restricted to age and gender as primary covariates.

Comprehensive medical histories, including current medication regimens and chronic systemic conditions, were systematically recorded. Age was stratified into three distinct categories: 35-40, 41-50, and 51-65 years.

Examiner calibration and reliability assessment

To establish intra-examiner reliability, a randomly selected sub-sample of 34 participants (comprising 20% of the study cohort) underwent a duplicate clinical examination by the same clinician three weeks post-baseline. Intra-examiner calibration demonstrated excellent reproducibility, with no statistically significant discrepancies between the timepoints (weighted Cohen's kappa=0.96). To preclude confounding of the calibration metrics, no oral hygiene instructions were provided during the inter-examination interval.

Clinical periodontal evaluation

All periodontal examinations were conducted in a standardized dental clinical setting utilizing a Williams periodontal probe with a calibrated probing force of 0.2 N (DB764R, Aesculap AG & Co. KG), a mouth mirror, and dental forceps under standardized illumination. Third molars and residual root fragments were excluded from the diagnostic protocol.

The periodontal assessment evaluated overall status *via* Probing Pocket Depth (PPD) and Clinical Attachment Loss (CAL). Measurements were recorded at four sites per tooth (mesiobuccal, distobuccal, mesiolingual, and distolingual) across all quadrants. For each parameter, the maximum value per tooth was documented to the nearest millimeter and subsequently dichotomized for multivariable statistical modeling.

Periodontal parameters were categorized according to the established staging criteria PPD, stratified into Stage I/II (maximum PPD≤4.0 mm or ≤5.0 mm, respectively, with predominant horizontal bone loss), and Stage III/IV (Stage III: PPD≥6.0 mm with vertical bone loss≥3.0 mm, Class II/III furcation involvement, or moderate ridge defects, and Stage IV, meeting Stage III criteria alongside complex rehabilitation requirements driven by masticatory dysfunction, secondary occlusal trauma, tooth mobility≥degree 2, severe ridge defects, bite collapse, tooth drifting/flaring, or <20 remaining teeth/10 opposing pairs) [53].

Clinical Attachment Loss (CAL), stratified into Stage I/II (interdental CAL at the site of greatest loss measuring 1-2.0 mm or 3-4.0 mm, respectively) and Stage III/IV (Stage III: interdental CAL at the site of greatest loss≥5.0 mm with a history of ≤4 teeth lost due to periodontitis; Stage IV: interdental CAL≥5.0 mm with a history of ≥5 teeth lost due to periodontitis) [53].

The number of missing teeth was stratified as none, 1-4, 5-10, >10 missing teeth [54].

Ethical considerations

Under national regulatory frameworks in Greece, institutional

ethical review and formal approval are mandatory primarily for interventional clinical trials or experimental studies conducted under the oversight of national health authorities. Because the present study was designed as a non-interventional, observational case-control investigation utilizing routine clinical examinations and questionnaire data, it did not strictly fall within the mandate for compulsory institutional ethical board review.

Nonetheless, the study protocol adhered to the ethical principles of the Declaration of Helsinki. All participants were comprehensively briefed regarding the objectives, risks, and procedural aspects of the investigation, and subsequent written informed consent was obtained from each individual prior to formal enrollment.

Results

The mean age of the study cohort was 46±4.7 years.

As already mentioned, individuals with grade III OG (anaplastic) were excluded from the study sample.

Univariate analysis revealed that a family history of OG (p=0.000) was significantly associated with an increased risk of OG development. Unadjusted Odds Ratios (ORs) and corresponding 95% Confidence Intervals (CIs) for all evaluated variables are detailed in Table 1.

In the initial stage of the multivariate logistic regression analysis (Step 1a - Enter step), a family history of the OG (p=0.000) was statistically significantly associated with the risk of tumor development. Adjusted ORs and 95% CIs for each parameter are comprehensive in Table 2. The final backward elimination step (Step 3a - Wald method) demonstrated that a family history of the disease (p=0.000) remained statistically significantly associated with the risk of tumor development, while younger age (p=0.076) and deeper periodontal pockets (p=0.089), demonstrated a non-statistically significant trend toward an increased risk of disease onset (Table 2).

Discussion

Over the past few decades, the association between PD, encompassing gingivitis and, predominantly, periodontitis, and the risk of oncogenesis has undergone extensive scientific investigation, frequently yielding discordant findings. As a chronic inflammatory pathology, PD is etiologically associated with a broad spectrum of systemic disorders [55-58]. A large body of epidemiological research have evaluated the association between oral health status and various malignancies.

Cumulative evidence consistently demonstrated that advanced periodontitis, exacerbated by subsequent tooth loss, was associated with an elevated risk of oncogenesis across heterogeneous populations [23, 27, 59-64]. Nonetheless, these epidemiological associations exhibit constrained clinical utility when utilized as standalone preventive indices [25]. Despite this prognostic limitation, the current literature provides critical insights emphasizing the potential therapeutic efficacy of timely periodontal interventions in reducing the incidence of specific anatomical site malignancies [65].

Following the application of the final step of the logistic regression analysis, a family history of the tumor was found to be statistically significantly associated with the risk of developing grade II OG. This finding was in accordance with those from previous reports [11, 12]. On the other hand, common epidemiological indices such as gender were found not to be associated with the risk of developing grade II OG. On the contrary previous studies showed a male-to-female predominance of approximately 2:1 [11, 12].

Regarding the age of tumor onset, previous investigations have demonstrated that it is prevalent in younger cohorts [2, 4]. These findings were in agreement with those of the current study, as this trend is reflected by the B coefficient (negative sign) across the stages of the logistic regression analysis.

Probing Pocket Depth (PPD) serves as a robust metric for assessing the clinical severity of PD [66], while concurrently acting as a reliable biomarker of active inflammatory status [67]. Our clinical findings demonstrated no statistically significant association between elevated PPD and the risk of developing grade II OG. Conversely, a recent report [41] indicated that an adverse periodontal profile, specifically a probing depth (PD)≥6.0 mm, was prevalent in 42.9% (9/21) of patients diagnosed with glioma, a rate significantly exceeding that observed in cohorts with benign tumors. The aforementioned

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	23 (54.8)	68 (54.0)	0.929	1.033 (0.512-2.082)
Females	19 (45.2)	58 (46.0)		
Age (years)				
35-40	11 (26.2)	35 (27.8)	0.935	———
41-50	17 (40.5)	47 (37.3)		
51-65	14 (33.3)	44 (34.9)		
OG family history				
Presence	18 (42.9)	11 (8.70)	0.000*	7.841 (3.286-18.707)
Absence	24 (57.1)	115 (91.3)		
Probing pocket depth				
Stage I/II	17 (40.5)	44 (34.4)	0.517	1.267 (0.619-2.595)
Stage III/IV	25 (54.5)	82 (65.1)		
Clinical Attachment				
Loss	15 (35.7)	52 (41.3)	0.524	0.791 (0.383-1.631)
Stage I/II	27 (64.3)	74 (58.7)		
Stage III/IV	-	-		
Number of missing teeth				
None	10 (23.8)	26 (20.6)	0.932	———
1-4 teeth	11 (26.2)	30 (23.8)		
5-10 teeth	14 (33.3)	45 (35.7)		
>10 teeth	7 (16.7)	25 (19.8)		
	-	-		

*p-value: statistically significant

Table 2: Presentation of association between potentially risk factors and CM according to Enter (first step-1a) and Wald (last step 3a) 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	-,009	,405	,001	1	,982	,991	,448	2,191
	Age.group	-,168	,243	,478	1	,189	,845	,524	1,362
	Family.history	2,022	,452	7,972	1	,000*	6,555	3,712	12,339
	Prob.pock.dep	1,461	,563	1,672	1	,112	1,630	,509	2,010
	Clin.att.loss	1,365	,554	1,434	1	,102	1,441	,486	2,272
	Num.miss.teeth	-,035	,204	,029	1	,866	,966	,647	1,442
	Constant	5,246	,779	5,624	1	,032	,288	-	-
Step 3[a]	Age.group	-,176	,236	,555	1	,076*	,819	,528	1,332
	Family.history	2,012	,449	7,102	1	,000*	7,479	4,103	13,022
	Prob.pock.dep	1,241	,402	1,360	1	,089*	1,786	,458	2,727
	Constant	5,195	,721	6,068	1	,005	,303	-	-

a. Variable(s) entered on step 1: gender, age.group, family.history, prob.pock.dep, clin.att.loss, num.miss.teeth.
*p - value: statistically significant.

study focused exclusively on grade I-IV gliomas, focused mainly on Glioblastomas as there are no other published papers investigating the association between PD and OG.

In contrast, Clinical Attachment Loss (CAL) represents a critical index for evaluating cumulative periodontal tissue destruction, thereby reflecting the long-term sequelae of chronic inflammatory episodes. Although both PPD and CAL pathophysiologically characterize the destructive phases of chronic periodontal inflammation [68], the present investigation did not reveal a statistically significant association between stage III/IV CAL and elevated grade II OG risk. To date, only that single study [41] has reported that an unfavorable periodontal status, characterized by an Attachment Loss (AL)>5.00 mm, was present in 42.9% (9/21) of glioma patients, which was significantly higher compared to individuals with benign lesions. However, as already mentioned the previous study focused on GB (grade IV glioma).

To date, no studies in the available literature have investigated the association between tooth loss and the risk of developing oligodendroglioma (grade II) or gliomas, in general. Although Michaud et al. [40] addressed brain tumors, the authors did not explicitly define the term 'brain malignancy'. Furthermore, their statistical analysis revealed no significant associations between the number of missing teeth and brain tumor risk (number of remaining teeth 17-24, HR=0.98, 95% CI=0.57-1.68, and HR=0.99, 95% CI=0.58-1.70, and number of remaining teeth 0-16, HR=1.28, 95% CI=0.65-2.51, and HR=1.31, 95% CI=0.66-2.59).

Nonetheless, these preliminary insights do not establish robust evidence of a causal relationship between PD and OG or other oncological malignancies. The precise biological mechanisms underpinning the implication of oral dysbiosis or PD in OG pathogenesis remain poorly elucidated, though several pathophysiological hypotheses regarding OG oncogenesis have been proposed.

Chronic inflammation represents a well-established enabling hallmark of oncogenesis [69]. Periodontitis, as a persistent infectious pathology, drives sustained low-grade systemic inflammation, which has been mechanistically implicated in both tumor initiation and progression [70-72]. Consequently, an essential role for immunoinflammatory cascades has been proposed, given that dysregulated inflammatory responses constitute a critical shared pathophysiological feature of both periodontal destruction and carcinogenesis [40].

Periodontal inflammatory disease and dental calculus are increasingly recognized as potential risk factors for human neoplasms, acting as primary drivers of localized and systemic inflammatory microenvironments that promote neoplastic transformation [69, 73, 74]. This chronic inflammatory state plays a pivotal role in oncogenesis, potentially by inhibiting apoptosis and promoting cell survival pathways [75].

Several molecular and cellular mechanisms have been proposed to elucidate the association between PD and malignancy. Specifically, advanced periodontitis may serve as a clinical surrogate marker of systemic immune dysfunction, reflecting impaired host immunosurveillance against tumor growth and metastatic progression [76]. Furthermore, inadequate oral hygiene and severe PD, frequently exacerbated by tobacco consumption and dietary factors, facilitate the synthesis of endogenous nitrosamines via nitrate-reducing oral bacteria [77-79]. Consequently, subsequent tooth loss resulting from compromised oral health may further accelerate the production of these carcinogenic nitrosamines [80].

Inflammatory processes further accelerate carcinogenesis by stimulating cellular proliferation and mutagenesis, compromising cellular adaptation to oxidative stress, orchestrating tumor angiogenesis, and upregulating the secretion of key inflammatory mediators, including specific cytokines and chemokines [81]. Concurrently, periodontitis is linked to disrupted antioxidant enzyme homeostasis [82]. Notably, the severity of periodontal destruction is linked with the upregulation of Glutathione Peroxidase 1 (GPX1) transcript levels. The subsequent oxidative and nitrosative stress derived from these sustained inflammatory cascades generates Reactive Oxygen Species (ROS) and Reactive Nitrogen Intermediates (RNI), potentially inducing genotoxic DNA mutations or impeding highly conserved DNA repair mechanisms [83].

Regarding the pathophysiological association between periodontitis and cerebral gliomas, emerging evidence implicates several distinct mechanisms. The first pathway involves hematogenous bacterial translocation. Specifically, periodontal pathogens, most notably Porphyromonas gingivalis, and their highly immunogenic shedding products, such as Lipopolysaccharides (LPS), can compromise the Blood-Brain Barrier (BBB) to gain access to the central nervous system [84]. Alternatively, oncogenic receptor activation represents a critical pathway, as recent molecular evidence demonstrates that *P. gingivalis*-derived LPS facilitates the proliferation and migration of glioma cells via the hyperactivation of the Akt signaling cascade. Lastly, sustained peripheral overproduction of pro-inflammatory cytokines and chemokines secondary to severe periodontitis drives chronic neuro-inflammation, chronically activating cerebral microglia and cultivating a highly permissive microenvironment that fosters tumor progression [85].

Discrepancies across published literature may come from variations in study design, cohort characteristics, or PD classification metrics. Conflicting findings are frequently attributable to baseline heterogeneities in study samples regarding age, gender, SES, educational attainment, tobacco smoking behaviors, and the precise extent and severity of PD. While most surveys controlled for the confounding effects of smoking via multivariate regression models utilizing a qualitative smoking covariate, other cohorts eliminated this specific confounder by strictly excluding smokers from the study population.

It is known that, confounding introduces systematic bias that investigators aim to eliminate or control within the effect estimate. Conversely, effect modification represents an intrinsic biological or epidemiological property of the specific exposure-outcome pathway under investigation. Consequently, tobacco use and other covariates, such as age, SES, and educational status, can function either as operational confounding factors or as genuine effect modifiers [86, 87].

The robust association of smoking with both PD pathogenesis and specific malignancies may account for the observed variations in cancer risk across distinct geographical regions, anatomical sites, and independent studies. However, the assessment of smoking intensity and duration within cohort studies is inherently subject to considerable measurement imprecision, where classification by smoking status often introduces non-differential misclassification or overlapping classifications. This methodological limitation may result in residual confounding due to incomplete control for tobacco exposure, thereby biasing the risk estimates of an intervening variable such as PD [88, 89].

The structural strengths and inherent limitations of the present investigation warrant careful consideration when interpreting the observed findings. Key strengths comprise the completeness of longitudinal follow-up and the utilization of a well-characterized cohort, which facilitated the rigorous evaluation of both confounding and effect modification by established risk factors, thereby minimizing the likelihood of biased associations. Furthermore, PD was defined based on objective clinical oral examinations rather than subjective self-reported data, substantially reducing the risk of exposure misclassification and reducing the potential underestimation of the evaluated associations.

Nevertheless, certain limitations must be acknowledged. In particular, the possibility of residual confounding cannot be entirely discounted, as the computed risk estimates may remain influenced by unmeasured, unquantified, or currently unknown confounding variables.

Conclusion

The current research showed that the presence of a family history of grade II OG was significantly associated with an increased risk of developing grade II OG, while younger age of individuals and deep periodontal pockets were positively, though non-significantly, associated with grade II OG risk.

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