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Periodontal Disease and Astrocytoma (grades I-III) Risk in Greek Adults: A Case-Control Study

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Abstract

Background/Aim: *Previous researches have revealed associations between Periodontal Disease and diverse types of cancer, such as oral/head and neck cancer, esophageal cancer, gastric cancer, lung cancer, kidney cancer, prostate cancer, hematological malignancies, etc... The current investigation aimed to examine the possible association between Periodontal Disease and the risk of Astrocytoma (grades I-III) development.*

Materials and Methods: *The sample of the present study was consisted of 45 individuals suffered from Astrocytoma (grades I-III) and 135 matching healthy individuals, who were recruited from one Dental and three Medical private practices. The participants completed a standardized health questionnaire, and underwent a clinical examination. Periodontal status was assessed using the following clinical indices probing pocket depth (PPD), and clinical attachment loss (CAL). Data analysis was performed using univariate and logistic regression models, with adjustments for potential confounders.*

Results: *The presence of Neurofibromatosis I (p= 0.000, OR= 6.083), and Li-Fraumeni syndromes (p=0.002, OR= 4.860) were significantly associated with an increased risk of developing Astrocytoma (grades I-III) compared to healthy controls. In contrast, CAL (p=0,054) was marginally statistically significant for the risk of Astrocytoma (grades I- III) development, whereas deeper periodontal pockets (PPD) (p=0.071, OR=1.749) were not statistically significant, after adjustment for confounding factors such as gender and age.*

Conclusions: *The current research suggested that after adjustment for age and gender, CAL demonstrated a borderline statistically significant association with Astrocytoma (grades I-III) risk whereas PPD did not retain statistical significance.*

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Introduction

Astrocytomas represent a prominent category of primary Central Nervous System (CNS) malignancies arising from neoplastic astrocytes, which constitute the star-shaped glial architecture of the brain parenchyma [1]. Epidemiological data indicate that these tumors account for approximately 75% of all diagnosed gliomas and encompass 25% to 30% of all primary intracranial neoplasms. Among malignant gliomas, glioblastoma, designated as Grade IV astrocytoma, exhibits the highest prevalence at 58.4%. This is followed by diffuse astrocytoma (7.3%), anaplastic astrocytoma (6.8%), oligodendroglioma (3.5%), anaplastic oligodendroglioma (1.7%), pilocytic astrocytoma (5.0%), and malignant gliomas not otherwise specified (NOS) at 7.9% (Louis et al.,2021).

The clinical manifestation and epidemiological distribution of astrocytomas vary significantly across demographic cohorts. In pediatric oncology, low-grade variants, predominantly pilocytic astrocytoma, are most frequently documented. Conversely, the adult population experiences a higher predominance of high-grade, aggressive phenotypes, including anaplastic astrocytoma and glioblastoma multiforme. Within adult cohorts, the age-adjusted incidence rate is critically elevated for glioblastoma, standing at 3.23 per 100,000 individuals, whereas diffuse and anaplastic astrocytomas present with lower rates of 0.46 and 0.42 per 100,000 individuals, respectively. Annually, approximately 15,000 novel astrocytoma cases are diagnosed in the United States, representing nearly half of all primary brain tumors. Furthermore, a distinct gender-based disparity is observable, with males displaying a slightly higher incidence compared to females, yielding a male-to-female ratio of 1.3-1.5:1 [1-3].

Histopathologically, the World Health Organization (WHO) classifies astrocytomas into four distinct grades that serve as critical prognostic indicators. Grade I (pilocytic astrocytoma) is associated with a favorable clinical prognosis, Grade II (diffuse astrocytoma) presents a moderate prognosis, Grade III (anaplastic astrocytoma) carries an unfavorable prognosis, and Grade IV (glioblastoma) is characterized by highly aggressive behavior and a poor clinical outcome (Louis et al., 2021). The incidence rates of these neoplasms are directly proportional to their histological severity. To be more specific, lower-grade malignancies (Grades I and II) occur less frequently, whereas high-grade forms-specifically Grade IV glioblastoma-exhibit a substantially higher epidemiological incidence [2, 3].

Risk factors for tumor development are genetic, environmental, and lifestyle-related. Hereditary and genetic risk factors encompass well-characterized cancer predisposition syndromes, most notably Li-Fraumeni,Turcot syndrome, Neurofibromatosis type I (NF1), and constitutional mismatch repair deficiency. Neurofibromatosis type 1, an autosomal dominant disorder caused by germline mutations in the NF1 tumor suppressor gene, exhibits a distinct pathogenic tropism for the CNS, as it is strongly associated with the clinical manifestation of brainstem astrocytomas, pilocytic astrocytomas, and various other intracranial malignancies. In addition to genetic susceptibility, environmental and exogenous factors significantly modulate oncogenic risk. Among these, exposure to ionizing radiation-particularly from therapeutic cranial radiotherapy administered during prior oncological interventions-constitutes the most robustly validated environmental risk factor. Conversely, occupational or accidental exposure to specific chemical agents, including vinyl chloride, petrochemical derivatives, and agricultural pesticides, alongside prolonged exposure to electromagnetic fields, have been investigated as potential carcinogens, though definitive epidemiological

evidence linking the latter astrocytoma development remains inconclusive [4-9].

Unlike other types of cancer, cigarette smoking does not seem to be associated with an increased risk of developing CNS tumors. This definitive epidemiological conclusion is strongly supported by extensive longitudinal cohort studies and comprehensive meta analyses that rigorously evaluated both the quantitative intensity and chronological duration of tobacco consumption cohorts. Additional potential risk factors include profound states of immunosuppression, which appear to marginally elevate oncogenic risk. This phenomenon is clinically documented in cohorts presenting with Human Immunodeficiency Virus (HIV) infection or individuals undergoing aggressive immunosuppressive therapeutic regimens. Furthermore, advanced age is associated directly with an increased incidence and susceptibility to high-grade, poor prognosis astrocytomas [10-12].

Periodontal Disease (PD), particularly in its severe form, periodontitis, is a chronic inflammatory condition affecting the supporting structures of the teeth. This condition is primarily initiated by a pathogenic bacterial dysbiosis within the gingival tissues, which subsequently propagates to the surrounding alveolar bone. As a consequence of a sustained, systemic host immuno-inflammatory response directed against pathogenic dental plaque biofilms, PD frequently contributes to a generalized state of low-grade systemic inflammation. This systemic involvement is characterized by significantly elevated circulating serum concentrations of pro-inflammatory biomarkers, including interleukin-6 (IL-6) and C-reactive protein (CRP) [13-15].

According to data compiled by the Global Burden of Disease (GBD) Study 2019, approximately 1.1 billion cases of severe periodontitis were documented globally, demonstrating a critical epidemiological surge compared to statistical estimates recorded in 1990. Beyond localized oral morbidity, PD is strongly associated with an expansive spectrum of systemic comorbidities, including Cardiovascular Diseases (CVD), Diabetes Mellitus (DM), Rheumatoid Arthritis, and multiple distinct types of malignancies. These profound systemic associations are partially elucidated by shared environmental or genetic risk factors, as well as common, overlapping hyper-inflammatory and biomolecular signaling pathways. Over the past few decades, substantial scientific attention has been directed toward elucidating the oncogenic implications of PD. Emerging epidemiological evidence robustly suggests that chronic periodontitis is associated not only with an elevated risk of overall cancer incidence but also with the pathogenesis of specific site-related malignancies. Concurrently, accumulating biomolecular evidence indicates a potential pathophysiological link between periodontal dysbiosis and the pathogenesis or clinical exacerbation of CNS disorders. Notably, Porphyromonas gingivalis, a keystone periodontal pathogen, has been isolated from post-mortem brain tissues of patients diagnosed with various neurological conditions, including Alzheimer's disease (AD) and intracranial aneurysms. Lipopolysaccharide (LPS) derived from P. gingivalis serves as a standardized experimental model to elucidate the systemic impact of PD on both oncological progression and CNS pathologies. Consistent with this invasive mechanism, the localization of P. gingivalis LPS within cerebral tissues has been definitively demonstrated via advanced immunofluorescence labeling [16-37].

Notably, only a limited number of epidemiological studies have specifically investigated PD as a potential risk factor or brain malignancies. A prospective cohort study focused on malignant sites rarely reported in association with periodontal pathologies yielded predominantly null findings regarding brain oncology, demonstrating an adjusted hazard ratio (HR) of 0.99 (95% CI, 0.61-1.59). Another similar research showed that poor periodontal status [probing depth (PPD) $\geq$ 6.0 mm and attachment loss (CAL) >5.0 mm] was found in 42.9% (9/21) of patients with glioma, which was significantly higher than that in patients with benign tumors. Moreover, a case-control study reported that the oral microbiota composition and gene functions are significantly associated with human brain glioma grade [38-40].

Despite a substantial number of prior studies, the reported associations between PD and cancer risk remain inconsistent, even after adjustment for potential confounding factors such as smoking, educational attainment, and socioeconomic status (SES). While the precise molecular mechanisms underlying these associations are not yet fully elucidated, several biochemical pathways have been proposed. Specifically, PD may modulate oncogenesis through sustained

systemic inflammatory responses mediated by circulating pro-inflammatory cytokines, the direct hematogenous translocation of oral pathogens into the bloodstream, and/or the systematic subversion of host immune surveillance [41, 42].

To date, no prospective or retrospective epidemiological studies have been conducted in Greece to examine the potential association between PD indices and astrocytoma risk. The present case-control study aims to investigate the relationship between PD indices and astrocytoma development in a cohort of Greek adults.

Materials and Methods

Design of the Study and Sample Size Estimation

This observational case-control investigation enrolled 180 participants (97 males and 83 females) within an age cohort spanning 40 to 78 years. The sample comprised 45 patients clinically diagnosed with histologically verified astrocytoma (Grades I-III) and 135 matched healthy controls. A priori statistical sample size determination was executed via the EpiTools web-based epidemiological platform [43]. This estimation was modeled on established astrocytoma prevalence rates, assuming a 95% confidence level and an 80% statistical power threshold. Participant recruitment was conducted across three specialized medical practices and one private dental practice during a a time period extending from April 2023 to March 2026. All enrolled individuals underwent comprehensive intraoral and dental clinical examinations, and subsequently completed a structured, standardized medical and periodontal diagnostic questionnaire. Clinical periodontal status was systematically classified in accordance with the age-specific methodological guidelines outlined by the WHO [44].

Eligibility Criteria for Cases and Controls

Eligibility required that both astrocytoma patients and controls had not received any periodontal treatment, surgical or non-surgical, within the preceding six months. In addition, participants must not have used systemic glucocorticoids, immunosuppressive agents, or systemic antibiotics during the same period. Inclusion criteria required the presence of more than 15 natural teeth and a diagnosis of periodontitis ranging from stage I to IV. Participants were excluded if they presented with systemic conditions known to influence periodontal status, including DM, CVD, acute pulmonary diseases such as chronic obstructive pulmonary disease (COPD), or any other malignancy, due to their potential confounding effects. To align socioeconomic and regional baselines, all participants were recruited from homogenous socio-professional environments, resided within the same urban area, and maintained routine follow-up at the participating clinical facilities. Furthermore, individuals belonging to the same familial lineages were systematically excluded to minimize the confounding implications of genetic clustering. To minimize selection and recall biases, controls were individuall matched to index cases at a 3:1 ratio based on age and biological gender, which represent established risk factors for periodontal tissue degradation and crucial confounding variables in multi-variable statistical modeling. Due to the adverse clinical course and poor prognosis, patients with Grade IV astrocyto (or Glioblastoma) were excluded from the study protocol [45-48].

Clinical Assessment and Diagnostic Procedures

The primary diagnosis of the tumor was based on Magnetic Resonance Imaging (MRI),however, definitive diagnosis was based on histopathological examination of the intra-operatively removed tumor or its parts, using traditional histological, cytologic and histo-chemical methods. In case the neurosurgical tumor resection was not possible, Fine Needle Aspiration (FNA) biopsy was performed. The study excluded individuals who underwent any form of treatment, such as surgery, radiotherapy, chemotherapy (target therapies such as BRAF/MEK or mTOR, or targeted IDH inhibitors etc.), immediately following the diagnosis of the disease, as this could have affected their periodontal status and the intra-examiner variance [49-51].

Data Collection and Confounder Assessment

Prior to periodontal examination, all participants completed a standardized, modified medical questionnaire [46]. To conserve statistical power and eliminate the risk of multi-collinearity within the multivariable regression models, age and biological gender were the primary covariates utilized for statistical adjustment. Broader socio-economic markers, including educational attainment and active tobacco consumption, were intentionally omitted from multivariate weighting due to the relatively small sample size of the astrocytoma cohort. Complete secondary medical histories, including chronic systemic comorbidities and concurrent maintenance pharmacotherapies, was systematically recorded. For stratified analyses, age parameters were

segregated into four distinct chronological cohorts: 40-49, 50-59, 60-69, and >70 years.

Reliability Assessment

Intra-examiner reliability was assessed in a randomly selected sub-sample of 36 participants (20% of the cohort), who were re-examined by the same clinician three weeks after the initial assessment. No significant differences were observed between measurements (Cohen's kappa = 0.95). No oral hygiene instructions were provided during the interval between examinations.

Periodontal Condition Evaluation

Periodontal examinations were performed in a dental clinical setting using a Williams periodontal probe with controlled probing force (0.2 N; DB764R, Aesculap AG & Co. KG), a mouth mirror, dental forceps, and a standardized dental light source. Third molars and residual root fragments were excluded from periodontal scoring.

The periodontal assessment included probing pocket depth (PPD), and clinical attachment loss (CAL) for the evaluation of overall periodontal status. All measurements were recorded at four sites per tooth (mesiobuccal, distobuccal, mesiolingual, and distolingual) in all quadrants. For each parameter, the highest recorded value per tooth was documented to the nearest millimeter and subsequently converted into dichotomous variables for statistical analysis. PPD was categorized as stage I/II (maximum probing depth ≤ 4.0 mm with mostly horizontal bone loss, and maximum probing depth ≤ 5.0 mm with the same one loss, respectively), and stage III/IV (in addition to stage II: probing depth ≥ 6.0 mm with vertical bone loss ≥ 3.0mm and furcation involvement Class II or III and moderate ridge defect, and in addition to stage III: need for complex rehabilitation due to: masticatory dysfunction, secondary occlusal trauma-tooth mobility degree ≥ 2-and severe ridge defect, bite collapse, drifting, flaring, and less than 20 remaining teeth-10 opposing pairs, respectively). Concurrently, CAL was classified as stage I/II (interdental CAL at site of greatest loss, 1-2.0 mm, and 3-4.0mm, respectively), and stage III/IV (interdental CAL at site of greatest loss, ≥ 5.0 mm with tooth loss ≤ 4 teeth, and ≥5.0mm with tooth loss with tooth loss ≥5.0 teeth, respectively) [52].

Ethical Considerations

In Greece, formal ethical approval is generally required for interventional or experimental clinical studies conducted under national health authority oversight. As the present study was designed as a retrospective case-control investigation based on clinical examinations and questionnaire data, it did not fall within the scope of mandatory institutional ethical review under these regulations.

All participants were fully informed regarding the objectives and procedures of the study and provided written informed consent prior to enrollment

Results

The mean age of the study sample was 57 ± 3.2 years.

The main histological types concerned Grade I astrocytoma (18.4%), Grade II (33.7%), and Grade III (47.9%).

Table 1 presents the outcomes after application of Univariate analysis, and showed that the presence of a Neurofibromatosis I history (p=0.000), and stage III/IV attachment loss (CAL) (p=0.027), were statistically significantly associated with risk for astrocytoma development. Table 1 also displays Unadjusted OR's and 95% CI for each variable analyzed. After application of the first step (step 1[a] –Enter method) of the logistic regression model it was found that a Neurofibromatosis I (p=0.000), and a Li-Fraumeni medical history (p=0.012), were significantly associated with risk of astrocytoma appearance (Table 2). Table 2 also demonstrates Adjusted OR's and 95% CI for each index examined. The final step (step 3[a]-Wald method) of the model showed (Table 2) that a Neurofibromatosis I (p=0.000), and a Li-Fraumeni medical history (p=0.002), and stage III/IV attachment loss (p=0.054), were statistically significantly associated with risk for developing astrocytoma, after adjusting for gender, and age.

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

Variables	Cases	Controls	p-value	Odds Ratio and 95% Confidence Interval
Gender				
Males	25 (55.6)	72 (53.3)	0.467	1.094 (0.555-2.155)
Females	20 (44.4)	63 (46.7)		
Age (years)				
40-49	12 (26.7)	28 (20.7)		
50-59	15 (33.3)	45 (33.3)	0.841	_____
60-69	10 (22.2)	36 (26.7)		
70+	8 (17.8)	26 (19.3)		
Neyrofibromatosis I history				
absence	18 (40.0)	102 (75.6)	0.000*	0.216 (0.106-0.440)
presence	27 (60.0)	33 (24.4)		
Li-Fraumeni history				
absence	36 (80.0)	121 (89.6)	0.082*	0.463 (0.185-1.157)
presence	9 (20.0)	14 (10.4)		
Probing pocket depth				
stage I/II	19 (42.2)	58 (43.0)	0.536	0.970 (0.490-1.920)
stage III/IV	26 (57.8)	77 (57.0)		
Clinical Attachment Loss				
stage I/II	14 (31.1)	66 (48.9)	0.027*	0.472 (0.231-0.966)
stage III/IV	31 (68.9)	69 (51.1)		

* 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.

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1a	gender	,281	,404	,483	1	,487	1,324	,600	2,926
	age. groups	,026	,189	,019	1	,892	1,026	,708	1,487
	Neurofi-brom.I	2,351	,482	11,805	1	,000*	7,498	4,083	12,997
	Li-Fraum. syndr	,856	,586	10,022	1	,012*	5,397	2,228	8,183
	Prob. Pock. Dep	,361	,413	2,292	1	,082	2,493	1,289	5,909
	Clin.Att. Loss	,442	,467	2,075	1	,064	2,390	1,156	4,973
	Constant	6,884	,592	13,750	1	,000	,056		
Step 3[a]	Neurofi-brom.I	2,311	,472	13,993	1	,000*	6,083	3,970	13,419
	Li-Fraum. syndr	1,768	,570	9,619	1	,002*	4,860	2,017	8,914
	Prob. Pock. Dep	,409	,460	6,899	1	,071	1,749	1,109	3,253
	Clin.Att. Loss	,938	,466	4,056	1	,054*	2,322	1,127	4,275
	Constant	6,698	,450	15,918	1	,000	,067		

Variables in the Equation

Variable(s) entered on step 1: gender, age.groups, Neurofibrom.I, LiFraum.syndr, Prob.Pock.Dep, Clin.Att. Loss.

* p-value: statistically significant

Discussion

Over the past few decades the pathophysiological association between PD, encompassing both gingivitis and chronic periodontitis, and systemic oncogenesis has been extensively investigated, frequently yielding heterogeneous and conflicting clinical results. As a destructive, chronic inflammatory pathology, PD is structurally linked to a wide array of systemic morbidities and multi-organ disorders. Numerous studies have explored the relationship between oral health status and various types of cancer. Most findings suggest that periodontitis, as well as tooth loss, was associated with an increased risk of several cancers across different populations [24, 25]. However, these associations have limited practical significance in terms of preventive indices [20], although they have provided valuable insights into the potential role of PD treatment in reducing the risk of certain cancers [53-63].

After adjustment for confounding factors, individuals with a Neurofibromatosis I, and Li-Fraumeni medical history, and PD variables such as stage III/IV CAL were statistically significantly associated with the risk of astrocytoma development. On the other hand, common epidemiological indices such as gender, and advanced age, were found not to be associated with the risk of developing astrocytoma.

The current report demonstrated that a medical history of the mentioned syndromes significantly increases Astrocytoma risk, finding that was in accordance with those from previous studies [4]. PPD serves as a clinically reliable metric for quantifying the severity of PD and functions as a direct indicator of active, acute localized inflammatory status [64, 65]. Our findings did not demonstrate a statistically significant association between increased PPD and the risk of developing astrocytoma. On the contrary, a recent report showed that poor periodontal status [probing depth (PPD) ≥ 6.0 mm] was found in 42.9% (9/21) of patients with glioma, which was significantly higher than that in patients with benign tumors [39].

In contrast to PPD, CAL represents a critical diagnostic index for evaluating cumulative, life-long periodontal tissue destruction, thereby reflecting the long-term historical impact of prior chronic inflammatory episodes. Although both PPD and CAL structurally characterize the destructive phases of chronic periodontitis, the current multivariate analysis revealed a statistically significant association exclusively between Stage III/IV CAL and an elevated risk of astrocytoma onset [66]. To date, only a singular study has demonstrated that an adverse periodontal status, defined by severe CAL >5.0 mm, was present in 42.9% of glioma patients compared to controls [39]. Nevertheless, these fragmented epidemiological associations do not yet provide robust, definitive evidence of a direct causal relationship between periodontal pathology and astrocytoma.

The precise biomolecular and cellular mechanisms underlying the implication of oral dysbiosis or chronic periodontitis in the pathogenesis of astrocytoma remain largely elusive. However, several interconnected pathophysiological hypotheses have been proposed to elucidate this oncogenic risk. Chronic, unresolving inflammation is a well-established hallmark of systemic carcinogenesis [67].

Periodontitis, functioning as a persistent infectious and immune-pathological disorder, promotes a continuous state of low-grade systemic inflammation, which has been mechanistically implicated in tumor initiation, cellular transformation, and malignant progression [68-70]. Consequently, a pivotal role for shared immuno-inflammatory and signaling pathways has been suggested, as localized tissue inflammation and systemic oncogenesis share overlapping biomolecular features [40].

Periodontal inflammatory disease and the accumulation of dental calculus have long been implicated as potential risk factors for systemic human carcinogenesis. This biological link is grounded in the principle that chronic inflammation constitutes a critical enabling hallmark of cancer and may act as an underlying driver of neoplastic transformation [67, 71, 72].

Chronic, unresolved inflammation plays a pivotal role in oncogenesis, potentially by inhibiting physiological apoptosis and promoting survival pathways in damaged cells. To elucidate the association between PD and malignancy, several molecular and immunological mechanisms have been proposed. Specifically, severe periodontitis may serve as a clinical marker of localized or systemic immune dysfunction, reflecting compromised host immune surveillance against early tumor growth and malignant progression. Furthermore, inadequate oral hygiene and active PD, frequently exacerbated by chronic tobacco consumption and adverse dietary habits, facilitate the localized proliferation of nitrate-reducing bacteria, thereby accelerating the endogenous synthesis f carcinogenic nitrosamines. Consequently, progressive tooth loss may further modify the oral microbiome, creating a microenvironment that further accelerates nitrosamine production [73-78].

Sustained inflammation further drives carcinogenesis by enhancing cellular proliferation, inducing mutagenesis, reducing cellular adaptation to oxidative stress, and promoting neo-angiogenesis. These processes are mediated by the hyper-secretion of inflammatory mediators, such as pro-inflammatory cytokines and chemokines. Moreover, periodontitis is associated with a distinct disruption of antioxidant enzyme activity within oral fluids. Increased severity of PD has been linked to elevated glutathione peroxidase 1 (GPX1) transcript levels. The cumulative oxidative and nitrosative stress generated by these chronic inflammatory cascades releases

highly reactive free radicals, such as reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI). These molecules are capable of inducing direct DNA mutations or systematically interfering with highly conserved DNA repair mechanisms [79-81]

Regarding the specific pathophysiological association between periodontitis and brain gliomas, emerging biomolecular evidence suggests that direct bacterial translocation may be a primary driver. Periodontal pathogens, most notably the keystone virulent species P. gingivalis, along with their circulating toxic byproducts, such as LPS, can directly enter the systemic bloodstream during mastication or oral hygiene procedures and subsequently compromise and cross the blood-brain barrier (BBB). Another compelling molecular mechanism involves targeted receptor activation. Current research has demonstrated that P. gingivalis-derived LPS can significantly facilitate the proliferation, oncogenic signaling, and cellular migration of human glioma cells via the hyper-activation of the intracellular Akt signaling pathway [39]. A final proposed mechanism focuses on the pathogenic role of chronic, low-grade neuroinflammation. The long-term peripheral overproduction and systemic circulation of pro-inflammatory cytokines and chemokines triggered by severe, unresolving periodontal tissue destruction are hypothesized to cross the BBB, subsequently activating cerebral microglia and fostering a pro-tumorigenic neuro-microenvironment that drives neoplastic progression [82, 83].

The documented methodological discrepancies across the literature often arise from variations in study design, heterogeneous cohort characteristics, or different PD clinical classification records. These conflicting epidemiological findings could be attributed to baseline differences in study samples regarding age, gender, SES, educational attainment, tobacco consumption behaviors, and the precise anatomical extent and clinical severity of periodontitis. While the majority of prior investigations adjusted for the confounding effects of smoking via multivariate regression models utilizing a qualitative, categorical smoking variable, alternative study designs eliminated this confounder entirely by excluding active smokers from the study population. Mechanistically, confounding introduces a systematic bias that investigators must mitigate or control within the effect estimate to prevent distorted associations. Conversely, effect modification represents an intrinsic biological or epidemiological property of the specific exposure-disease interaction under investigation. Consequently, tobacco consumption and other sociodemographic variables, such as age, SES, and educational status, can function either as traditional confounding factors or as true effect modifiers depending on the underlying biological framework [84, 85].

The strong association of smoking with PD and with some cancers may account for some of the variations in cancer risk between regions/sites and across studies. Assessment of intensity and duration in a cohort study is subject to considerable measurement imprecision, and classification by smoking status can create indistinct borders. This may result in incomplete control for the impact of smoking and bias estimates of an intervening variable like periodontal disease [86-87]. The strengths and limitations of the present study should be carefully considered when interpreting the observed findings. Key strengths include the completeness of follow-up and the use of a well-characterized cohort, which enabled the assessment of both confounding and interaction by established risk factors, thereby minimizing the likelihood of biased associations. Furthermore, PD was defined based on clinical oral examination rather than self-reported data, reducing the risk of exposure misclassification and the potential underestimation of the association under investigation. Nevertheless, certain limitations should be acknowledged. In particular, the possibility of residual confounding cannot be excluded, as risk estimates may still be influenced by unmeasured or unknown confounders.

Conclusions

The current research showed that the presence of a Neurofibromatosis, and Li-Fraumeni syndromes medical history, and stages III/IV of clinical attachment loss were significantly associated with an increased risk of developing Astrocytoma.

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