



Is Periodontal Disease a Risk Factor for Meningioma (WHO Grade I and II)? A Clinical and Questionnaire - Based Case - Control Study

Nikolaos Andreas Chrysanthakopoulos^{1,2,3*}, Panagiotis Andreas Chrysanthakopoulos⁴ and Vassiliki Vazintari⁵

¹Dental Surgeon (DDSc), Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Department of Pathological Anatomy, Medical School, University of Athens, Athens, Greece

²Resident in Maxillofacial and Oral Surgery, 401 General Military Hospital of Athens, Athens, Greece

³Ph. D. in Oncology (Cand), Registrar in Dentistry, NHS of Greece, Greece

⁴MD, Neurosurgeon of Greek Armed Forces, former Director of the Neurosurgical Department of NIMTS Military Hospital of Athens, Athens, Greece

⁵MD, Registrar in Pathology, Ilioupoli Health Centre - NHS of Greece, Athens, Greece



OPEN ACCESS

*Correspondence:

Dr. Nikolaos Andreas Chrysanthakopoulos, Dental Surgeon (DDSc), Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Department of Pathological Anatomy, Medical School, University of Athens, Athens, Greece; E-mail: nikolaos_c@hotmail.com; nchrysant@med.uoa.gr

Received Date: 28 Aug 2026

Accepted Date: 26 Sep 2026

Published Date: 28 Sep 2026

Citation:

Chrysanthakopoulos NA, Chrysanthakopoulos PA, Vazintari V. Is Periodontal Disease a Risk Factor for Meningioma (WHO Grade I and II)? A Clinical and Questionnaire - Based Case - Control Study. WebLog J Neurosurg. wjns.2026.i2801. <https://doi.org/10.5281/zenodo.23298691>

Copyright© 2026 Dr. Nikolaos Andreas Chrysanthakopoulos. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background/Aim: Although periodontal disease has been epidemiologically linked to various systemic malignancies, comprehensive literature regarding its specific association with brain tumors remains scarce. The primary objective of this study was to investigate the potential association of periodontal disease with the risk of meningioma, (WHO Grade I and II), development.

Materials and Methods: This retrospective case-control study enrolled 74 individuals with newly diagnosed meningioma (WHO grade I and II) and 148 age- and gender matched healthy controls. Prior to the initiation of any oncological intervention, all participants completed a standardized health questionnaire and underwent a rigorous clinical periodontal assessment. Periodontal health status was quantified utilizing Probing Pocket Depth (PPD), and Clinical Attachment Loss (CAL). To isolate the independent association between periodontal status and meningioma (WHO grade I and II) risk, data were subjected to univariate and multivariate logistic regression analyses, adjusting for potential confounding covariates.

Results: Following adjustment for gender, age, and smoking status, multivariate analysis revealed that patients with an elevated BMI ($p=0.470$, OR=1.562), exhibited a statistically significant predisposition toward an elevated risk of meningioma (WHO grade I and II) development, and these with more severe CAL (stages III/IV) ($p=0.072$, OR=1.386), were marginally associated with the risk of tumor development, associations that remained after adjustment for age, gender, and smoking history.

Conclusions: Patients with higher BMI, and advanced CAL were positively associated with the risk of developing meningioma (WHO grade I and II).

Keywords: Meningioma (WHO Grade I, and II); Periodontal Disease; Adults

Introduction

Meningioma (MG) represents the most prevalent primary neoplasm of the Central Nervous System (CNS), accounting for approximately one-third (37.1% to 37.6%) of all primary intracranial and CNS malignancies [1, 2]. In the United States, the annual age-adjusted incidence rate of MGs ranges between 8.33 and 8.58 per 100,000 person-years, according to data published by the Central Brain Tumor Registry of the US (CBTRUS) [2, 3]. The incidence of MGs exhibits a direct, linear association with advancing age, demonstrating a pronounced escalation within the geriatric population, particularly after the age of 65 years [1, 2, 4-6]. While predominantly manifesting during the sixth and seventh decades of life, MGs remain exceedingly rare in pediatric cohorts, comprising merely 0.4% to 4.1% of all childhood CNS neoplasms [4]. Among adults, a distinct female predominance is well-documented. MGs classified as World Health Organization (WHO) grades 1 and 2 collectively exhibit a 2.27-fold to 2.3-fold higher prevalence in female cohorts

compared to males [2, 3].

Advanced age and genetic susceptibility constitute well-established risk factors for MG development [7, 8]. Ionizing radiation represents a primary causative factor, with a well-documented pathogenic association observed not only after therapeutic irradiation for a variety of medical indications but also among atomic bomb survivor cohorts [7-9]. Beyond high-dose radiation regimens, exposure to therapeutic low-dose radiation (1-2 Gy), particularly during childhood, is strongly associated with an elevated risk of MG development [10]. Characteristically, radiation-induced MGs frequently present as multi-focal tumors and exhibit aggressive clinicopathological features [8, 10]. Additional potential risk factors currently under investigation include craniocerebral trauma, tobacco smoking, higher Body Mass Index, and specific viral etiologies [7, 11-15].

Neurofibromatosis type 2 (NF2) constitutes the most prevalent hereditary genetic syndrome predisposing individuals to MG development. Notably, patients presenting with NF2 exhibit a significantly higher propensity for developing atypical to malignant variants (WHO grades 2 and 3) as well as multifocal MGs [16].

A multitude of investigations suggest a strong endocrine-mediated influence on the pathogenesis and oncogenesis of MGs [14, 17]. This hormonal hypothesis is heavily supported by several clinical observations, including the elevated incidence rates in females of reproductive age, a documented epidemiological association with breast carcinoma, and discernible variations in tumor volume during pregnancy, the menstrual cycle, and menopause. On a molecular level, approximately 76% of benign MGs demonstrate robust tumoral expression of progesterone receptors [14, 17]. Furthermore, prolonged female exposure to exogenous progesterone has been associated with down-regulated levels of progesterone receptor and NF2 mRNA expression in peripheral blood, suggesting a potential mechanistic link to an elevated risk of MG development [18].

Anatomically, the vast majority of MGs are intracranial (79.8%), whereas spinal locations account for a distinct minority of 4.2% [3]. These neoplasms histologically originate from meningotheial arachnoid cells, which exhibit divergent embryological derivatives based on their precise anatomical distribution [19]. Specifically, the meninges of the cerebral convexity embryonically derive from the neural crest, whereas those of the skull base originate from mesodermal structures [19, 20]. This distinct ontogenetic divergence significantly influences not only the heterogeneous histological phenotypes but also dictates the specific profiles of recurrent somatic mutations observed in these tumors [19, 20].

According to the revised 2016 WHO classification of CNS tumors, MGs are categorized into three distinct histological grades based on their malignant potential and clinical behavior [21, 22]. The vast majority of cases, approximately 80%, are classified as grade I, characteristically exhibiting benign histopathological features and an indolent clinical course [21]. Conversely, the remaining subset of tumors (20%) represents higher-grade malignancies, specifically grades II and III, which are defined by atypical to malignant histopathological features and demonstrate a significantly more aggressive clinical progression [3, 20].

A hallmark characteristic of MGs is the profound heterogeneity of their histopathological phenotypes, which encompasses 15 distinct variants stratified across the three WHO grades [18]. WHO grade I

(benign) encompasses nine variants, among which the meningotheial, fibrous, and transitional subtypes are the most frequently encountered. The psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and meta-plastic variants are also classified under this benign classification [22]. In contrast, WHO grades II and III each comprise three specific variants [22]. The atypical, chordoid, and clear cell variants are assigned to grade II, whereas the anaplastic (malignant), paillary, and rhabdoid variants are classified as grade III [22]. While each variant is definitively diagnosed based on pathognomonic histological morphology, a substantial number of MGs exhibit a mixed histological architecture within the same tumor mass. In such instances, the definitive diagnosis is dictated by the predominant histopathological pattern. During the 1970s, the loss of chromosome 22 was first documented *via* fluorescence techniques as a hallmark recurrent genetic alteration in MGs [23]. Subsequently, several rare familial syndromes predisposing individuals to MG development were identified, most notably NF2 [24]. In the 1990s, mutational inactivation of the NF2 gene localized on chromosome 22 was established as a primary oncogenic driver, occurring in 40% to 60% of sporadic MGs [25]. Following this discovery, intensive efforts to elucidate alternative candidate driver genes in NF2 wild-type MGs persisted. However, no critical genetic drivers were identified until 2013. Driven by advancements in Whole-Genome Sequencing (WGS) technologies, a distinct cohort of recurrent genetic drivers has since been uncovered, including Tumor necrosis Factor Receptor-Associated Factor 7 (TRAF7), Kruppel-Like Factor 4 (KLF4), v-Akt murine thymoma viral oncogene homolog1 (AKT1), and smoothed, frizzled class receptor (SMO) [26, 27].

Furthermore, in 2016, somatic mutations in the Phosphatidylinositol-4,5-bisphosphate 3-Kinase Catalytic subunit Alpha (PIK3CA) gene were also identified as a recurrent driving mechanism in a subset of MGs [28].

To date, surgical intervention remains the cornerstone of therapeutic management, with approximately 70% to 80% of MGs being effectively eradicated via surgical resection [20]. The most reliable prognostic indices for MGs constitute the histological grade (WHO classification) and the extent of surgical resection (Simpson grading system) [20, 29, 30]. Following macroscopically complete resection, the 5-year recurrence rates for WHO grade I, II, and III neoplasms are documented at 5%-10%, 50%, and 80%, respectively [31].

Periodontal Disease (PD), encompassing the distinct clinical phases of gingivitis and periodontitis, constitutes a progressive chronic inflammatory pathology that affects roughly 15% of the global adult cohort. Serving as the primary etiological agents, pathogenic oral bacteria [32] and concomitant viral entities [33] infiltrate the gingival tissues and supporting structures, triggering a severe host tissue reaction. The epidemiological effect and severity of PD is associated directly with tobacco abuse, inadequate oral hygiene, and advanced age. This pathological cascade induces the development of periodontal pockets, clinical attachment loss, gingival hemorrhage, and the destruction of alveolar bone architecture, with rapidly progressive clinical features leading to total tooth loss. Additionally, the complex interplay between immunodeficiency conditions, bone mineral density depletion (osteoporosis), and specific virulent profiles of the oral microbiome continues to be extensively evaluated [34, 35].

Far from being a strictly localized phenomenon, periodontal infection induces pronounced systemic sequelae across multiple

vital organ systems, including the cardiovascular and pulmonary tracts [36]. The driving pathophysiological mechanism involves the overproduction of Reactive Oxygen Species (ROS) and the subsequent induction of oxidative stress. This state is further mediated by reciprocal interactions with acute-phase cytokines and chemokines, specifically Interleukin (IL)-1, IL-6, and C-Reactive Protein (CRP), which actively dictate PD progression and severity [37]. The systemic effect of these inflammatory biomarkers is hypothesized to arise from a generalized low-grade inflammatory state, a systemic immune response directed against periodontal pathogens, or the direct translocation of oral microflora into the systemic circulation [38, 39].

Consequently, a vast body of epidemiological literature has extensively investigated periodontitis as an independent risk factor for systemic pathologies, establishing robust associations with atherosclerotic cardiovascular disease, stroke, Chronic Obstructive Pulmonary Disease (COPD), type 2 diabetes mellitus, rheumatoid arthritis, and various oncological conditions [35, 40-47].

An elevated risk of overall oncological susceptibility [48, 49], as well as site-specific malignancies [50-52], has been strongly associated with compromised oral health, advanced PD, and tooth loss, remaining independent of traditional confounding elements such as age, gender, tobacco use, and Socioeconomic Status (SES). Although extensive research has investigated the potential etiopathogenic and oncogenic influence of PD across multiple anatomical regions, including the oral cavity, esophagus, stomach, pancreas, and lungs [49, 53-56], the definitive nature of these findings remains a subject of ongoing investigation, even after rigorous adjustment for confounders. While shared immunoinflammatory and molecular pathways are hypothesized to drive both PD and malignant transformation, the precise pathophysiological mechanisms linking PD to cancer development remain to be fully elucidated.

To date, no prospective or retrospective epidemiological investigations in Greece have systematically evaluated the potential association between PD indices and the risk of developing MG (WHO grade I and II).

Consequently, the present case-control study was carried out to investigate the hypothetical relationship between clinical periodontal parameters and MG (WHO grade I and II) pathogenesis among Greek adult cohorts.

Materials and Methods

Study population and epidemiological design

A multi-center, retrospective case-control study was conducted between October 2024 and June 2026 across diverse clinical settings. To ensure statistical validity, sample size estimation was performed in strict accordance with baseline the tumors of the CNS prevalence data [57] and the EPITOOLS methodological guidelines [58] (ausvet.com.au), utilizing a 95% Confidence Interval (CI) and a statistical power of 0.80. Age-based stratification was aligned with the epidemiological recommendations of the WHO [59] for assessing CNS tumor incidence [60].

The total study population encompassed 222 participants of both genders, aged between 50 and 84 years, who were recruited from private medical, dental, and neurological clinics. The disease cohort comprised 74 patients with histologically validated MGs. The control cohort consisted of 148 healthy individuals. To establish a robust baseline and attenuate the confounding effects of gender, age, and

tobacco consumption, neighborhood and social-network controls were utilized. The control group was precisely frequency-matched to the case group by age and gender. Furthermore, to minimize selection bias, all participants were sampled from the same urban geographical region. Controls were selected from individuals undergoing routine health screenings at the participating medical sites during the 2024-2026 study period.

Diagnostic workflow and histopathological verification

The diagnostic procedure for suspected MG cases followed a standardized clinical protocol. Initial presumptive diagnosis was established via high-resolution contrast-enhanced Magnetic Resonance Imaging (MRI), identifying characteristic extra-axial dural-based lesions. Following radiological identification, all patients underwent surgical intervention (craniotomy for tumor resection). During the operative procedure, intraoperative frozen section analysis was utilized when necessary to provide immediate, preliminary histopathological guidance. Definitive and final diagnosis, however, was achieved postoperatively. The resected tumor specimens were subjected to formal histopathological and immunohistochemical evaluation. Tumors were histologically graded and classified in strict accordance with the updated WHO classification guidelines for CNS tumors [57,61].

Control selection and covariate matching

To ensure a homogenous study population, strict eligibility criteria were established for both the disease and healthy control cohorts. Eligible cases comprised patients with newly diagnosed, histopathologically verified MGs, in strict accordance with the current WHO diagnostic classification [57]. For the patient cohort, comprehensive clinical characteristics, tumor staging, and diagnostic parameters were extracted directly from verified institutional medical and neurooncological registries.

To attenuate confounding systemic influences on the biological markers under investigation, strict pharmacological and medical exclusion thresholds were enforced. Participants in both cohorts were excluded if they had received systemic antibiotic therapy, immunosuppressive regimens, or systemic glucocorticoids within the six months prior to enrollment. Furthermore, individuals who underwent conservative or surgical periodontal interventions within the preceding six-month period were deemed ineligible. Concurrently, a history of diabetes mellitus, severe cardiovascular pathology, rheumatoid arthritis, acute pulmonary disorders, or any secondary primary malignancy served as a basis for exclusion. These systemic conditions were strictly controlled for, as they are established factors that alter oral microbial profiles and periodontal tissue indices, which would introduce significant secondary analytical biases [62].

Within the patient cohort, specific neurooncological exclusion parameters were systematically applied. Patients presenting with advanced metastatic disease secondary to a primary malignancy originating outside the CNS, as well as those with secondary intracranial malignancies associated with multi-field carcinogenesis frameworks [63], were excluded from the study. Additionally, to guarantee unbiased baseline evaluations, MG patients were excluded if they had initiated any first-line oncological modalities, including surgical resection/stereotactic radiosurgery, fractionated radiotherapy, possible targeted chemotherapy/hormone-based therapy, prior to baseline data collection.

Selection and matching of the control cohort

To optimize statistical power and control for epidemiological variances, cases and controls were precision-matched in a 1:2 ratio. Matching covariates included gender, age (within a ± 4.5 -year window), and tobacco consumption (stratified as current/former, or never-smokers). Precise adjustment for these variables was mandatory, as they represent principal risk factors for systemic inflammation and potential sources of epidemiological confounding [64-67].

Clinical data collection and epidemiological survey

All eligible individuals within the disease and healthy control cohorts completed an adapted version of the Minnesota Dental School Medical Questionnaire [68]. This standardized questionnaire was administered to systematically gather comprehensive data regarding the participants' medical and dental history, current systemic comorbidities, and demographic determinants.

Definition and classification of covariates

Socio-demographic attributes were incorporated as potential confounding covariates in the subsequent statistical analyses. Age for both cases and controls was stratified into four distinct age cohorts: 50-59, 60-69, 70-79, and >80 years.

Due to the relatively small case sample size, SES, and educational attainment, were not included in the multivariable models to prevent multicollinearity and overfitting. Consequently, statistical adjustment for residual confounding was restricted to age and gender as primary covariates.

Tobacco consumption was evaluated and stratified into two primary operational categories, never-smokers (defined as individuals who had consumed fewer than 100 cigarettes during their lifetime) and active/former smokers (defined as individuals with a cumulative lifetime consumption of at least 100 cigarettes, further subdivided into current daily or occasional smokers, and those reporting sustained smoking cessation). Obesity was quantified utilizing the BMI, with participants stratified into normal ($<30 \text{ kg/m}^2$) and high ($\geq 30 \text{ kg/m}^2$) adiposity cohorts [15].

Clinical periodontal evaluation and diagnostic indices

Comprehensive oral and periodontal clinical measurements were performed by a calibrated Dental Surgeon. All examinations were conducted within a standardized clinical environment utilizing a uniform dental light source, a mouth mirror, and a specialized, pressure-sensitive periodontal probe with a defined spring-loaded probing force of 0.2 N (UNC15/ Williams type, model DB764R, Aesculap AG & Co. KG, Tuttlingen, Germany) to eliminate subjective intra-examiner measurement variance. To isolate chronic periodontal tissue parameters and prevent acute anatomical confounding, all remained roots and third molars were systematically excluded from scoring across all examined quadrants.

The baseline periodontal profile was established through the concurrent mapping of the following standard diagnostic indices, Probing Pocket Depth (PPD), and Clinical Attachment Loss (CAL). To optimize diagnostic sensitivity, measurements were systematically recorded across all dental quadrants. For each individual tooth, clinical indices were recorded across six designated sites, mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual, and distolingual. The highest recorded scores per index were calibrated to the nearest millimeter and binarized to serve as categorical predictors in the

statistical analysis.

Periodontal parameters were categorized based on established diagnostic staging frameworks. PPD values were stratified into Stage I/II and Stage III/IV cohorts. Stage I and II classifications were defined by a maximum PPD of $\leq 4.0 \text{ mm}$ and $\leq 5.0 \text{ mm}$, respectively, combined with a prevalence of horizontal bone resorption. Conversely, Stage III classification was characterized by a PPD reaching or exceeding 6.0 mm, vertical osseous defects of $\geq 3.0 \text{ mm}$, Class II or III furcation involvements, or moderate alveolar ridge deformities. Progression to Stage IV was determined when Stage III diagnostic thresholds were met in conjunction with severe functional impairments necessitating complex oral rehabilitation. These secondary complications included masticatory dysfunction, secondary occlusal trauma, advanced tooth mobility ($\geq \text{degree } 2$), severe ridge defects, bite collapse, pathologic tooth migration or flaring, or a depleted dentition consisting of fewer than 20 remaining teeth (or fewer than 10 opposing pairs) [69].

Assessment of CAL was assessed in accordance with standardized staging thresholds. Participants were stratified into either Stage I/II or Stage III/IV categories. The less severe categories (Stages I and II) were designated based on proximal CAL metrics at the zone of maximal tissue deficit, ranging from 1.0-2.0 mm and 3.0-4.0 mm, respectively. In contrast, classification within the advanced stages, III and IV, required an inter-dental CAL of 5.0 mm or greater at the site of maximal destruction. Differentiation between these two advanced categories was contingent upon the extent of secondary tooth mortality attributable to periodontitis. Cases presenting with a cumulative loss of 4 or fewer teeth were designated as Stage III, whereas a history of 5 or more missing teeth secondary to periodontal pathology defined the Stage IV cohort [69].

Methodological standardization and intra-examiner reproducibility

To verify the reproducibility of the clinical parameters and systematically quantify potential intra-examiner measurement variability, a randomly selected subset of 45 participants, constituting 20% of the total study population, was enrolled in a replication analysis. These subjects underwent a blinded clinical re-evaluation performed by the initial examining Dental Surgeon following a three-week stabilization period. Statistical reproducibility between the baseline and follow-up examinations revealed an exceptional level of reproducibility, evidenced by a computed Cohen's Kappa coefficient of 0.97. Notably, to maintain the baseline oral microenvironment and prevent transient behavioral confounding that could confound periodontal scoring outcomes, no oral hygiene counseling or instructions were administered to the participants during this interim three-week evaluation period.

Ethical compliance and informed consent

Given its design as a non-experimental, retrospective observational investigation, the study protocol complied with the institutional frameworks governing retrospective registry-based analyses. The research was conducted in strict adherence to the ethical principles outlined in the Declaration of Helsinki. Prior to enrollment, all participants received a comprehensive briefing detailing the study's specific objectives, clinical significance, and methodological workflow, and subsequently provided voluntary written informed consent.

Results

The mean ages were 64.5 ± 2.5 years and 62.4 ± 2.3 years for MG

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	40 (54.1)	77 (52.0)	0.776	1.085 (0.620-1.898)
Females	34 (45.9)	71 (48.0)		
Age				
50-59	13 (17.6)	32 (21.6)	0.732	-
60-69	26 (35.1)	49 (33.1)		
70-79	23 (31.1)	38 (25.7)		
80+	12 (16.2)	29 (19.6)		
Smoking				
Never smokers	25 (33.8)	59 (39.9)	0.378	0.770 (0.429-1.379)
Previous/ current smokers	49 (66.2)	89 (60.1)		
Body Mass Index				
<30 kg/m ²	27 (36.5)	70 (47.3)	0.126	0.640 (0.361-1.135)
≥30 kg/m ²	47 (63.5)	78 (52.7)		
Probing pocket depth				
Stage I/II	31 (41.9)	71 (48.0)	0.391	0.782 (0.445-1.373)
Stage III/IV	43 (58.1)	77 (52.0)		
Clinical Attachment Loss				
Stage I/II	28 (37.8)	65 (43.9)	0.387	0.777 (0.439-1.376)
Stage III/IV	46 (62.2)	83 (56.1)		

patients and healthy individuals, respectively.

The histological subtypes identified were meningothelial (67%) and fibrous (fibroblastic) (33%).

Univariate model was used to compare indices between patients and controls for categorical variables. No statistically significant associations were observed between the examined periodontal indices and the risk of meningioma development (Table 1). The same Table

displays Unadjusted OR's and 95% CI.

Following the application of the logistic regression model (Wald method), a high BMI was found to be statistically significantly associated with the risk of meningioma development ($p=0.047$), whereas CAL demonstrated a borderline significant association with this risk ($p=0.072$) (Table 2). Adjusted OR's and 95% CI are also detailed in the same Table.

Discussion

The most frequently utilized parameters for assessing periodontal status encompass clinical indices such as PPD, CAL, GI, Plaque Index (PII), BOP, Bleeding Point Index (BPI), Alveolar Bone Loss (ABL), and the number of missing or remaining teeth [70].

Within recent decades, the potential association between PD, including both gingivitis and, more notably, advanced periodontitis, and the risk of oncogenesis has been the subject of rigorous academic investigation, often producing conflicting outcomes. Characterized as a chronic inflammatory condition, PD is etiological linked to a diverse array of systemic pathologies [71-74]. Consequently, a substantial body of epidemiological research have sought to analyze the connection between oral health condition and different types of malignancies. A growing consensus in the literature indicates that severe periodontitis, which is frequently compounded by subsequent tooth loss, is associated with an increased susceptibility to cancer across diverse demographics [75-82]. However, these epidemiological relationships offer limited clinical utility when implemented as independent preventive parameters [47]. Notwithstanding these prognostic constraints, contemporary research offers valuable evidence highlighting that timely periodontal therapies could play a critical role in decreasing the incidence of specific anatomical site cancers [83].

To the best of our knowledge, the current literature contains no prior investigations exploring the potential link between tooth loss and the development of MGs. While Michaud *et al.*, [49] evaluated CNS neoplasms, their study focused on using the general term 'glioma' for the definition of the term "brain malignancy." Additionally, their statistical evaluations yielded no statistically significant association between dentition reduction and brain tumor susceptibility (for 17-

Table 2: Presentation of association between periodontal disease indices and meningioma (WHO grade I and II) development according to Enter (first step-1^a) and Wald (last step 6^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	,243	,294	,237	1	,326	1,154	,649	2,052
	age.group	,185	,146	,121	1	,872	1,075	,755	1,338
	smok.status	,217	,263	,224	1	,422	1,275	,704	2,309
	body.mass.ind	,429	,304	1,988	1	,089	1,536	,846	2,790
	prob.pock.dep	,162	,314	,266	1	,355	1,176	,636	2,174
	clin.att.loss	,410	,311	1,851	1	,102	1,332	,687	2,206
	Constant	1,224	,452	7,351	1	,007	,294		
Step 6 ^a	body.mass.ind	,446	,292	2,330	1	,047*	1,562	,881	2,770
	clin.att.loss	,423	,227	1,883	1	,072*	1,386	,693	2,254
	Constant	1,693	,542	8,702	1	,000	,500		

a. Variable(s) entered on step 1: gender, age.group, smok.status, body.mass.ind, prob.pock.dep, clin.att.loss.

*p-value: Statistically significant

24 remaining teeth: HR= 0.98, 95% CI =0.57-1.68, and HR=0.99, 95% CI=0.58-1.70, and for 0-16 remaining teeth: HR=1.28, 95% CI=0.65-2.51, and HR=1.31, 95% CI=0.66-2.59).

The findings revealed that patients with an elevated BMI ($p=0.470$, OR=1.562), exhibited a statistically significant predisposition toward an elevated risk of MG (WHO grade I and II) development, and these with more severe CAL (stages III/IV) ($p=0.072$, OR=1.386), more severe CAL (stages III/IV) ($p=0.072$, OR=1.386), were marginally associated with the risk of tumor development, associations that remained after adjustment for age, gender, and smoking history.

MG incidence is significantly higher in females and shows a sharp increase with advancing age [1, 2, 4, 6]. However, the current study did not confirm such associations, although age and gender are considered confounding factors [84].

Tobacco smoking is acknowledged as a potential risk factor for both the initiation and progression of PD and various malignancies [85]. Nonetheless, it frequently functions as a confounding variable in investigations evaluating the potential association between PD and cancer types where smoking etiologically contributes to oncogenesis.

Available evidence from broad epidemiological cohorts and systematic reviews suggested that tobacco consumption was not definitively recognized as a universal risk factor for the pathogenesis of MGs. Interestingly, the current literature highlights a notable divergence in this relationship when stratified by gender. Among male populations, a documented history of smoking was positively associated with an increased susceptibility to MG development (e.g., RR=1.42, 95% CI:1.16-1.74) [86]. In contrast, investigations focused on female cohorts frequently report neutral or inverse correlations. In fact, certain data paradoxically indicated a slight protective outcome, an effect that may be mediated by the anti-estrogenic properties inherent to tobacco components (e.g., OR=0.83, 95% CI: 0.70-0.98) [87]. The current study indicated no association between tobacco consumption and the risk of MG (WHO grade I and II) development.

Obesity and mainly raised BMI have been constantly associated with an increased risk of diverse type of cancers, such as breast [88], and Colorectal Cancer (CRC) [89]. The results recorded that patients with higher values of BMI were significantly associated with an elevated risk of MG (WHO grade I and II) development. This finding has been confirmed by a previous report [15], whereas a similar one did not confirm such an association [11]. PPD reflects the destructive pathology of a chronic inflammatory response and serves as an established indicator for assessing the severity of PD [90]. The outcomes demonstrated that PPD was not statistically significantly associated with an increased risk of MG (WHO grade I and II) development. This finding cannot be confirmed by previous reports as similar reports have not been carried out. On the contrary, a prospective study [49] reported no significant association between PD and risk of the tumor development although it refers to malignant brain tumors by employing the general term "glioma". CAL constitutes another critical index for assessing periodontitis severity [90], reflecting the long-term stages of chronic inflammation and the cumulative manifestations of destructive inflammatory processes. PPD and CAL reflect the long-term stages of chronic inflammation, encompassing the cumulative manifestations of destructive inflammatory processes [91]. The present study showed that patients with more severe CAL (stages III/IV), were marginally associated with the risk of tumor development, an association that remained

after adjustment for age, gender, and smoking history. Moreover, equivalent findings regarding the CAL index have not been previously documented by other investigators regarding patients with MGs.

Hujoel *et al.*, [54] hypothesized that gingival inflammation could potentially serve as an etiological risk factor for the development of several malignancies, such as lung cancer. It should be emphasized that patients with grade III MGs were excluded from the present study, as their behavior and poorer prognosis would negatively affect their selection and compliance in conducting the research. The possible worse PD indices in those patients could be raised from psychological burden, rather than from nutritional deficiencies, alterations in salivary quality and quantity, or disruptions in oral microbial and immunological homeostasis induced by chemotherapy or radiotherapy [92, 93], as the clinical progression of this stage is extremely unfavorable [94]. Furthermore, these patients may exhibit increased susceptibility to the progression and destruction of periodontal tissue compared to healthy individuals.

Although several pathophysiological hypotheses have been suggested, a definitive causal link between PD and CNS malignancies, such as MGs and gliomas, has yet to be fully established, leaving the exact molecular pathways largely unresolved.

Nevertheless, growing evidence underscores that oncogenesis is heavily driven by chronic inflammation. In this context, periodontitis functions as a persistent, low-grade infectious and inflammatory state that actively drives tumor initiation and progression [95-97]. This persistent microenvironment participates in neoplastic transformation by upregulating cell survival pathways and inhibiting apoptosis [53, 98-100].

Furthermore, advanced PD can be viewed as a clinical surrogate marker for systemic immune dysregulation, signifying a compromised host immunosurveillance system that fails to inhibit tumor expansion and metastatic dissemination. Concurrently, poor oral hygiene and severe tissue destruction, often compounded by tobacco use and dietary habits, promote the endogenous synthesis of carcinogenic nitrosamines through nitrate-reducing oral microbiota, a process further accelerated by subsequent tooth loss [87, 101-103].

At the molecular level, these sustained inflammatory processes accelerate carcinogenesis by driving cellular proliferation, mutagenesis, and tumor angiogenesis via the secretion of key cytokines and chemokines [104]. This state is coupled with a disruption in antioxidant enzyme homeostasis, where increased Glutathione Peroxidase 1 (GPX1) transcript levels reflect elevated oxidative and nitrosative stress [105]. The resulting generation of Reactive Oxygen Species (ROS) and Reactive Nitrogen Intermediates (RNI) induces genotoxic DNA mutations and impairs highly conserved DNA repair pathways [106].

The potential pathogenetic mechanisms concern direct bacterial invasion and blood-brain barrier (BBB) disruption, systemic inflammation and microglial activation, activation of oncogenic pathways and apoptosis suppression, and immune evasion and surveillance bypass.

The primary pathway connecting oral dysbiosis to CNS oncogenesis involves hematogenous bacterial translocation. Primary periodontopathogens, most notably *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, enter the bloodstream through ulcerated gingival tissues during bacteremia. These pathogens and their highly

immunogenic shedding products, such as Lipopolysaccharides (LPS), compromise and cross the BBB to infiltrate the CNS [107]. Regarding MGs, because the meninges (dura, arachnoid, and pia mater) are anatomically in direct contact with the cranial vasculature, chronic exposure of these cells to such microbes induces severe cellular stress and genotoxic mutations [107, 108].

According to the second potential mechanism periodontitis acts as a permanent "open wound" that floods the circulation with systemic inflammatory mediators. The shedding of LPS from Gram-negative oral bacteria activates host Toll-Like Receptors (TLRs), triggering an overproduction of pro-inflammatory cytokines, including IL-1 β , IL-6, TNF- α , and C-Reactive Protein (CRP) [109]. Upon crossing into the brain, these peripheral mediators stimulate cerebral microglial cells, triggering chronic neuroinflammation. This process establishes a highly permissive, chronic inflammatory microenvironment that promotes oncogenesis and drives the proliferation and progression of both glioma and MG cells [109, 110].

The third mechanism focuses on the fact that oral pathogens possess the distinct capacity to interfere with the physiological life cycle and signaling network of host cells. Molecular evidence demonstrates that *F. nucleatum* and *P. gingivalis* hyperactivate key intracellular signaling cascades, specifically the NF- κ B signaling pathway and the STAT3 protein [111].

Additionally, *P. gingivalis*-derived LPS drives the hyperactivation of the Akt signaling cascade, resulting in a significant increase in the expression of oncogenic mediators such as TNF- α , TGF- β , MMP2, and MMP9. Together, these molecular alterations are directly linked to enhanced tumor cell survival, accelerated migration, active angiogenesis, and the strict suppression of programmed cell death (apoptosis) [110, 111]. The last mechanism suggests that beyond driving proliferation, periodontal bacteria secrete specialized virulence factors that actively disrupt, degrade, or suppress the host's localized immune response, such as through the enzymatic degradation of immunoglobulins and complement factors [111]. The resulting systemic immunosuppression and compromised immunosurveillance enable mutated meningeal or glioma cells to successfully bypass host immune detection, facilitating their uninhibited survival, clonal expansion, and subsequent development into solid tumors [70, 111, 112].

Discrepancies across the published literature may stem from variations in study design, cohort characteristics, or PD classification criteria. Such conflicting findings are frequently attributable to baseline heterogeneities within study samples regarding age, gender, SES, educational status, tobacco smoking behaviors, and the exact staging and grading of PD. Although most studies adjusted for the confounding effects of smoking through multivariate regression models utilizing a qualitative smoking covariate, other cohorts controlled for this specific confounder by strictly excluding smokers from the study population. Even though confounding introduces systematic bias that investigators aim to reduce or minimize within the effect estimate, effect modification represents an intrinsic biological or epidemiological property of the specific exposure-outcome pathway under investigation. Consequently, tobacco smoking and other covariates, including age, SES, and educational attainment can function either as operational confounding factors or as genuine effect modifiers [55, 113].

The strong association of tobacco use with both PD pathogenesis

and particular malignancies may explain the observed variations in oncological risk across diverse geographical areas, anatomical sites, and independent investigations. Nonetheless, evaluating smoking intensity and duration within cohort studies is inherently prone to substantial measurement imprecision, as categorization by smoking status frequently introduces non-differential misclassification or overlapping strata. This methodological constraint can lead to residual confounding stemming from the incomplete adjustment for tobacco exposure, subsequently biasing the risk estimates of an intervening variable such as PD [114, 115].

The methodological strengths and inherent limitations of this study warrant careful consideration when interpreting the findings. Notable strengths include a complete longitudinal follow-up and the utilization of a well-characterized cohort, which enabled a rigorous evaluation of both confounding and effect modification by established risk factors, thereby minimizing the likelihood of biased associations. Additionally, PD was defined using standardized clinical oral examinations rather than subjective, self-reported data, substantially eliminating the risk of exposure misclassification and preventing the potential underestimation of the observed relationships.

Certain drawbacks, however, must be taken into account. Specifically, the potential for residual confounding cannot be completely ruled out, given that the calculated risk estimates might remain susceptible to unmeasured, unquantified, or as yet unidentified latent variables.

Conclusions

Individuals with higher BMI, and advanced CAL were positively associated with the risk of developing MG (WHO grade I and II), after adjustment for age, gender and tobacco consumption.

References

1. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol*. 2010; 99: 307-314.
2. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. *Neuro Oncol*. 2019; 21: v1-v100.
3. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro Oncol* 2018; 20: iv1- iv86.
4. Tufan K, Dogulu F, Kurt G, Emmez H, Ceviker N, Baykaner MK. Intracranial meningiomas of childhood and adolescence. *Pediatr Neurosurg*. 2005; 41(1): 1-7.
5. Bartek J, Sjøvik K, Förander P, Solheim O, Gulati S, Weber C, et al. Predictors of severe complications in intracranial meningioma surgery: a population-based multicenter study. *World Neurosurg*. 2015; 83: 673-678.
6. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro Oncol*. 2015; 17: iv1-iv62.
7. Galani V, Lampri E, Varouktsi A, Alexiou G, Mitselou A, Kyritsis AP. Genetic and epigenetic alterations in meningiomas. *Clin Neurol Neurosurg*. 2017; 158: 119-125.
8. Sadetzki S, Flint-Richter P, Ben-Tal T, Nass D. Radiation-induced meningioma: a descriptive study of 253 cases. *J Neurosurg*. 2002; 97(5): 1078-82.

9. Brenner AV, Sugiyama H, Preston DL, Sakata R, French B, Sadakane A, et al. Radiation risk of central nervous system tumors in the Life Span Study of atomic bomb survivors, 1958-2009. *Eur J Epidemiol.* 2020; 35(6): 591-600.
10. Phillips LE, Frankenfeld CL, Drangsholt M, Koepsell TD, van Belle G, Longstreth WT Jr. Intracranial meningioma and ionizing radiation in medical and occupational settings. *Neurology.* 2005; 64(2): 350-352.
11. Schneider B, Pülhorn H, Röhrig B, Rainov NG. Predisposing conditions and risk factors for development of symptomatic meningioma in adults. *Cancer Detect Prev.* 2005; 29(5):440-447.
12. Flint-Richter P, Mandelzweig L, Oberman B, Sadetzki S. Possible interaction between ionizing radiation, smoking, and gender in the causation of meningioma. *Neuro Oncol.* 2011; 13(3): 345-352.
13. Phillips LE, Koepsell TD, van Belle G, Kukull WA, Gehrels JA, Longstreth WT Jr. History of head trauma and risk of intracranial meningioma: population-based case control study. *Neurology.* 2002;58(12):1849-1852.
14. Huisman TW, Tanghe HL, Koper JW, Reubi JC, Foekens JA, Avezaat CJ, et al. Progesterone, oestradiol, somatostatin and epidermal growth factor receptors on human meningiomas and their CT characteristics. *Eur J Cancer.* 1991; 27(11): 1453-1457.
15. Muskens IS, Wu AH, Porcel J, Cheng I, Le Marchand L, Wiemels JL, et al. Body mass index, comorbidities, and hormonal factors in relation to meningioma in an ethnically diverse population: the Multiethnic Cohort. *Neuro Oncol.* 2019; 21(4):498-507.
16. Abi Jaoude S, Peyre M, Degos V, Goutagny S, Parfait B, Kalamarides M. Validation of a scoring system to evaluate the risk of rapid growth of intracranial meningiomas in neurofibromatosis type 2 patients. *J Neurosurg.* 2020;134(5): 1377-1385.
17. Sioka C, Kyritsis AP. Chemotherapy, hormonal therapy, and immunotherapy for recurrent meningiomas. *J Neurooncol.* 2009; 92(1): 1-6.
18. Supartoto A, Sasongk MB, Respatika D, Mahayana IT, Pawiroranu S, Kusnanto H, et al. Relationships Between Neurofibromatosis-2, Progesterone Receptor Expression, the Use of Exogenous Progesterone, and Risk of Orbitocranial Meningioma in Females. *Front Oncol.* 2019; 8: 651.
19. Kalamarides M, Stemmer-Rachamimov AO, Niwa-Kawakita M, Chareyre F, Taranchon E, Han ZY, et al. Identification of a progenitor cell of origin capable of generating diverse meningioma histological subtypes. *Oncogene.* 2011; 30(20): 2333-2344.
20. Preusser M, Brastianos PK, Mawrin C. Advances in meningioma genetics: novel therapeutic opportunities. *Nat Rev Neurol.* 2018; 14(2): 106-115.
21. Suppiah S, Nassiri F, Bi WL, Dunn IF, Hanemann CO, Horbinski CM, et al. Molecular and translational advances in meningiomas. *Neuro Oncol.* 2019; 21: i4-i17.
22. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO classification of tumours of the central nervous system. Revised 4th ed. International Agency for Research on Cancer. 2016.
23. Zankl H, Zang KD. Cytological and cytogenetical studies on brain tumors. Identification of the missing G chromosome in human meningiomas as no. 22 by fluorescence technique. *Humangenetik.* 1972; 14(2): 167-169.
24. Proctor DT, Ramachandran S, Lama S, Sutherland GR. Towards Molecular Classification of Meningioma: Evolving Treatment and Diagnostic Paradigms. *World Neurosurg.* 2018; 119: 366-373.
25. Rutledge MH, Sarrazin J, Rangaratnam S, Phelan CM, Twist E, Merel P, et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. *Nat Genet.* 1994; 6(2): 180-184.
26. Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, Ozduman K, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science.* 2013; 339(6123): 1077-1080.
27. Brastianos PK, Horowitz PM, Santagata S, Jones RT, McKenna A, Getz G, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet.* 2013; 45(3): 285-289.
28. Abedalthagafi M, Bi WL, Aizer AA, Merrill PH, Brewster R, Agarwalla PK, et al. Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma. *Neuro Oncol.* 2016; 18(5): 649-655.
29. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. *J Neurol Neurosurg Psychiatry.* 1957; 20(1): 22-39.
30. Gousias K, Schramm J, Simon M. The Simpson grading revisited: aggressive surgery and its place in modern meningioma management. *J Neurosurg.* 2016;125(3):551-560.
31. Yuzawa S, Nishihara H, Tanaka S. Genetic landscape of meningioma. *Brain Tumor Pathol.* 2016;33(4):237-247.
32. Loesche WJ, Grossman NS. Periodontal disease as a specific, albeit chronic, infection: diagnosis and treatment. *Clin Microbiol Rev.* 2001; 14(4): 727-752.
33. Grinde B, Olsen I. The role of viruses in oral disease. *J Oral Microbiol.* 2010; 12; 2.
34. Ramos Peña DE, Pillet S, Grupioni Lourenço A, Pozzetto B, Bourlet T, Motta ACF. Human immunodeficiency virus and oral microbiota: mutual influence on the establishment of a viral gingival reservoir in individuals under antiretroviral therapy. *Front Cell Infect Microbiol.* 2024; 14: 1364002.
35. Kim J, Amar S. Periodontal disease and systemic conditions: a bidirectional relationship. *Odontology.* 2006; 94(1): 10-21.
36. Papapanou PN. Periodontal diseases: epidemiology. *Ann Periodontol.* 1996; 1(1): 1-36.
37. Pouliou C, Piperi C. Advances of Oxidative Stress Impact in Periodontitis: Biomarkers and Effective Targeting Options. *Curr Med Chem.* 2024; 31(38): 6187-6203.
38. Renvert S, Lindahl C, Roos-Jansäker AM, Lessem J. Short-term effects of an anti-inflammatory treatment on clinical parameters and serum levels of C-reactive protein and proinflammatory cytokines in subjects with periodontitis. *J Periodontol.* 2009; 80(6): 892-900. doi: 10.1902/jop.2009.080552.
39. Vidal F, Figueredo CM, Cordovil I, Fischer RG. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension. *J Periodontol.* 2009; 80(5): 786-791.
40. Cullinan MP, Ford PJ, Seymour GJ. Periodontal disease and systemic health: current status. *Aust Dent J.* 2009; 54: S62-S69.
41. Holmstrup P, Poulsen AH, Andersen L, Skuldbøl T, Fiehn NE. Oral infections and systemic diseases. *Dent Clin North Am.* 2003; 47(3): 575-98.
42. Si Y, Fan H, Song Y, Zhou X, Zhang J, Wang Z. Association between periodontitis and chronic obstructive pulmonary disease in a Chinese population. *J Periodontol.* 2012; 83(10): 1288-1296.
43. Genco R, Offenbacher S, Beck J. Periodontal disease and cardiovascular disease: epidemiology and possible mechanisms. *J Am Dent Assoc.* 2002; 133: 14S-22S.
44. Joshupura KJ, Hung HC, Rimm EB, Willett WC, Ascherio A. Periodontal disease, tooth loss, and incidence of ischemic stroke. *Stroke.* 2003; 34(1): 47-52.
45. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. *Ann Periodontol.* 2003; 8(1): 54-69.

46. Ortiz P, Bissada NF, Palomo L, Han YW, Al-Zahrani MS, Panneerselvam A, et al. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. *J Periodontol*. 2009 ;80 (4): 535-540.
47. Fitzpatrick SG, Katz J. The association between periodontal disease and cancer: a review of the literature. *J Dent*. 2010; 38(2): 83-95.
48. Wen BW, Tsai CS, Lin CL, Chang YJ, Lee CF, Hsu CH, et al. Cancer risk among gingivitis and periodontitis patients: a nationwide cohort study. *QJM*. 2014; 107 (4): 283-290.
49. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshupura K. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. *Lancet Oncol*. 2008; 9(6): 550-558.
50. Tezal M, Sullivan MA, Hyland A, Marshall JR, Stoler D, Reid ME, et al. Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(9): 2406-2412.
51. Abnet CC, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Prospective study of tooth loss and incident esophageal and gastric cancers in China. *Cancer Causes Control*. 2001; 12(9): 847-854.
52. Stolzenberg-Solomon RZ, Dodd KW, Blaser MJ, Virtamo J, Taylor PR, Albanes D. Tooth loss, pancreatic cancer, and *Helicobacter pylori*. *Am J Clin Nutr*. 2003 ;78 (1): 176-181.
53. Michaud DS, Joshupura K, Giovannucci E, Fuchs CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. *J Natl Cancer Inst*. 2007; 99(2): 171-175.
54. Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. *Ann Epidemiol*. 2003; 13(5): 312-316.
55. Abnet CC, Qiao YL, Dawsey SM, Dong ZW, Taylor PR, Mark SD. Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort. *Int J Epidemiol*. 2005; 34(2): 467-474.
56. Rosenquist K, Wennerberg J, Schildt EB, Bladström A, Göran Hansson B, Andersson G. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Otolaryngol*. 2005; 125(12): 1327-1336.
57. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021; 23(8): 1231-1251.
58. Villarta RL, Asaad AS. Sample Size Determination in an Epidemiologic Study using the EpiTools Web-Based Calculator. *Acta Medica Philippina*. 2014; 48(1): 42-46.
59. World Health Organization. Oral health surveys: basic methods. 1997.
60. Mesfin FB, Karsonovich T, Al-Dhahir MA. Gliomas. *StatPearls*. 2024.
61. Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD, Lukas RV. An overview of meningiomas. *Future Oncol*. 2018 ;14(21): 2161-2177.
62. Machuca G, Segura-Egea JJ, Jiménez-Beato G, Lacalle JR, Bullón P. Clinical indicators of periodontal disease in patients with coronary heart disease: a 10 years longitudinal study. *Med Oral Patol Oral Cir Bucal*. 2012; 17(4): e569-e574.
63. Rubin H. Fields and field cancerization: the preneoplastic origins of cancer: asymptomatic hyperplastic fields are precursors of neoplasia, and their progression to tumors can be tracked by saturation density in culture. *Bioessays*. 2011; 33(3): 224-231.
64. Reichert S, Stein J, Gautsch A, Schaller HG, Machulla HK. Gender differences in HLA phenotype frequencies found in German patients with generalized aggressive periodontitis and chronic periodontitis. *Oral Microbiol Immunol*. 2002;17(6): 360-368.
65. Lavstedt S, Bolin A, Henrikson CO. Proximal alveolar bone loss in a longitudinal radiographic investigation.II. A10-year follow-up study of an epidemiologic material. *Acta Odontol Scand*. 1986; 44(4): 199-205.
66. Tonetti MS, Claffey N. European Workshop in Periodontology group C. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. Group C consensus report of the 5th European Workshop in Periodontology. *J Clin Periodontol*. 2005; 32: 210-213.
67. Loos BG, John RP, Laine ML. Identification of genetic risk factors for periodontitis and possible mechanisms of action. *J Clin Periodontol*. 2005; 32: 159-179.
68. Molloy J, Wolff LF, Lopez-Guzman A, Hodges JS. The association of periodontal disease parameters with systemic medical conditions and tobacco use. *J Clin Periodontol*. 2004; 31(8): 625-632.
69. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol*. 2018; 45: S162-S170.
70. Meyer MS, Joshupura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. *Cancer Causes Control*. 2008; 19(9): 895-907.
71. Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. *Int Dent J*. 2009; 59(4): 197-209.
72. de Oliveira Ferreira R, de Brito Silva R, Magno MB, Carvalho Almeida APCPS, Fagundes NCF, Maia LC, et al. Does periodontitis represent a risk factor for rheumatoid arthritis? A systematic review and meta-analysis. *Ther Adv Musculoskelet Dis*. 2019; 11: 1759720X19858514.
73. Moghadam SA, Shirzaiy M, Risbaf S. The Associations between Periodontitis and Respiratory Disease. *J Nepal Health Res Council*. 2017; 15(1): 1-6.
74. Helenius-Hietala J, Suominen AL, Ruokonen H, Knuuttila M, Puukka P, Jula A, et al. Periodontitis is associated with incident chronic liver disease-A population-based cohort study. *Liver Int*. 2019; 39(3): 583-591.
75. Chen Y, Zhu BL, Wu CC, Lin RF, Zhang X. Periodontal Disease and Tooth Loss Are Associated with Lung Cancer Risk. *Biomed Res Int*. 2020; 2020: 5107696.
76. Michaud DS, Fu Z, Shi J, Chung M. Periodontal Disease, Tooth Loss, and Cancer Risk. *Epidemiol Rev*. 2017; 39(1): 49-58.
77. Zeng XT, Xia LY, Zhang YG, Li S, Leng WD, Kwong JS. Periodontal Disease and Incident Lung Cancer Risk: A Meta-Analysis of Cohort Studies. *J Periodontol*. 2016; 87(10): 1158-1164.
78. Al-Maweri SA, Ibraheem WI, Al-Ak'hali MS, Shamala A, Halboub E, Alhaji MN. Association of periodontitis and tooth loss with liver cancer: A systematic review. *Crit Rev Oncol Hematol*. 2021; 159: 103221.
79. Chen H, Nie S, Zhu Y, Lu M. Teeth loss, teeth brushing and esophageal carcinoma: a systematic review and meta-analysis. *Sci Rep*. 2015; 5: 15203.
80. Hiraki A, Matsuo K, Suzuki T, Kawase T, Tajima K. Teeth loss and risk of cancer at 14 common sites in Japanese. *Cancer Epidemiol Biomarkers Prev*. 2008 ;17(5): 1222-1227.
81. Lee K, Lee JS, Kim J, Lee H, Chang Y, Woo HG, et al. Oral health and gastrointestinal cancer: A nationwide cohort study. *J Clin Periodontol*. 2020 ;47(7): 796-808.
82. Momen-Heravi F, Babic A, Tworoger SS, Zhang L, Wu K, Smith-Warner SA, et al. Periodontal disease, tooth loss and colorectal cancer risk: Results from the Nurses' Health Study. *Int J Cancer*. 2017; 140(3): 646-652.
83. Hwang IM, Sun LM, Lin CL, Lee CF, Kao CH. Periodontal disease with treatment reduces subsequent cancer risks. *QJM*. 2014; 107(10): 805-812.
84. Selvaraj RC, Cioffi G, Waite KA, Jackson SS, Barnholtz-Sloan JS. A Pan-

- Cancer Analysis of Age and Sex Differences in Cancer Incidence and Survival in the United States, 2001-2020. *Cancers*. 2025; 17(3): 378.
85. Nair J, Ohshima H, Nair UJ, Bartsch H. Endogenous formation of nitrosamines and oxidative DNA-damaging agents in tobacco users. *Crit Rev Toxicol*. 1996; 26(2): 149-161.
 86. Chao H, Cheng Y, Shan J, Xue HF, Xu WL, Li HJ, et al. A meta-analysis of active smoking and risk of meningioma. *Tob Induc Dis*. 2021; 19: 34.
 87. Zhong P, Lin Y, Chen T. A decreased risk of meningioma in women smokers was only observed in American studies rather than studies conducted in other countries: a systematic review and meta-analysis. *Chin Neurosurg J*. 2021; 7(1): 45.
 88. Arnold M, Pandeya N, Byrnes G, Renehan PAG, Stevens GA, Ezzati PM, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol*. 2015; 16(1): 36-46.
 89. Safizadeh F, Mandic M, Schöttker B, Hoffmeister M, Brenner H. Central obesity may account for most of the colorectal cancer risk linked to obesity: evidence from the UK Biobank prospective cohort. *Int J Obes*. 2025; 49(4): 619-626.
 90. Zimmermann H, Hagenfeld D, Diercke K, El-Sayed N, Fricke J, Greiser KH, et al. Pocket depth and bleeding on probing and their associations with dental, lifestyle, socio-economic and blood variables: a cross-sectional, multicenter feasibility study of the German National Cohort. *BMC Oral Health*. 2015; 15: 7.
 91. Miskiewicz A, Szparecki G, Durlak M, Rydzewska G, Ziobrowski I, Górka R. The correlation between pancreatic dysfunction markers and selected indices of periodontitis. *Adv Clin Exp Med*. 2018; 27(3): 313-319.
 92. Pearman T. Psychosocial factors in lung cancer: quality of life, economic impact, and survivorship implications. *J Psychosoc Oncol*. 2008; 26(1): 69-80.
 93. Dyszkiewicz Konwinska M, Mehr K, Owecka M, Kulczyk T. Oral Health Status in Patients Undergoing Chemotherapy for Lung Cancer. *Open J Dent Oral Med*. 2014; 2: 17-21.
 94. Sá-Marta E, Alves JL, Rebelo O, Barbosa M. World Health Organization Grade III Meningiomas: A Retrospective Study at an Academic Medical Center. *World Neurosurg*. 2021; 149: e877-e893.
 95. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002; 420(6917): 860-867.
 96. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001; 357(9255): 539-545.
 97. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008; 454(7203): 436-444.
 98. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144(5): 646-674.
 99. Hanahan D. Hallmarks of Cancer: New Dimensions. *Cancer Discov*. 2022; 12(1): 31-46.
 100. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000; 100(1): 57-70.
 101. Shapiro KB, Hotchkiss JH, Roe DA. Quantitative relationship between oral nitrate-reducing activity and the endogenous formation of N-nitrosoamino acids in humans. *Food Chem Toxicol*. 1991; 29(11): 751-755.
 102. Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. *J Natl Cancer Inst*. 2003; 95(13): 948-960.
 103. Abnet CC, Kamangar F, Dawsey SM, Stolzenberg-Solomon RZ, Albanes D, Pietinen P, et al. Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. *Scand J Gastroenterol*. 2005; 40(6): 681-687.
 104. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med*. 2010; 49(11): 1603-1616.
 105. Toczewska J, Baczyńska D, Zalewska A, Maciejczyk M, Konopka T. The mRNA expression of genes encoding selected antioxidant enzymes and thioredoxin, and the concentrations of their protein products in gingival crevicular fluid and saliva during periodontitis. *Dent Med Probl*. 2023; 60(2): 255-265.
 106. Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. *Int J Cancer*. 2007; 121(11): 2381-2386.
 107. Baima G, Minoli M, Michaud DS, Aimetti M, Sanz M, Loos BG, et al. Periodontitis and risk of cancer: Mechanistic evidence. *Periodontol*. 2024; 96(1): 83-94.
 108. Wang S, Tian Y, Wu Y, Yu Z, Zhang J, Zhang J, Liu S. *Fusobacterium nucleatum* bacteremia complicated with intracranial *Porphyromonas gingivalis* and HSV-1 infection: a case report and literature review. *BMC Infect Dis*. 2024; 24(1): 225.
 109. Huang JH, Chen Y, Kang YB, Yao ZJ, Song JH. The potential crosstalk genes and molecular mechanisms between glioblastoma and periodontitis. *Sci Rep*. 2024; 14(1): 5970.
 110. Hashioka S, Inoue K, Miyaoka T, Hayashida M, Wake R, Oh-Nishi A, et al. The Possible Causal Link of Periodontitis to Neuropsychiatric Disorders: More Than Psychosocial Mechanisms. *Int J Mol Sci*. 2019; 20(15): 3723.
 111. Guo J. Pathogenic Mechanisms of Periodontal Pathogens: Implications for Diagnosis and Therapy. *Theoretical and Natural Science*. 2025; 137: 113-117.
 112. Gao Z, Weng X, Yu D, Pan Z, Zhao M, Cheng B, et al. *Porphyromonas gingivalis*-Derived Lipopolysaccharide Promotes Glioma Cell Proliferation and Migration via Activating Akt Signaling Pathways. *Cells*. 2022; 11(24): 4088.
 113. Yao SG, Fine JB. Periodontitis and cancer...a link? A review of the recent literature. *Compend Contin Educ Dent*. 2010; 31(6): 436-442.
 114. Marshall JR, Hastrup JL. Mismeasurement and the resonance of strong confounders: uncorrelated errors. *Am J Epidemiol*. 1996; 143(10): 1069-1078.
 115. Marshall JR, Hastrup JL, Ross JS. Mismeasurement and the resonance of strong confounders: correlated errors. *Am J Epidemiol*. 1999; 150(1): 88-96.