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An Investigation of the Association Between Periodontal Disease and Cutaneous Melanoma: A Case-Control Study in Greek Adults

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Abstract

Background/Aim: Previous investigations have showed biological linkages between Periodontal Disease and various types of cancer, such as oral/head and neck cancer, gastric cancer, esophageal cancer, kidney cancer, lung cancer, prostate cancer, hematological malignancies, and cutaneous melanoma. This research investigation aimed to assess the possible association between Periodontal Disease indices and the risk of Cutaneous Melanoma.

Materials and Methods: The current case-control study was consisted of 86 individuals suffered from Cutaneous Melanoma and 172 matching healthy ones, who were recruited from one Dental and two Medical private practices, and completed a standardized health questionnaire, and clinically examined. Periodontal status comprised the following clinical indices Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Gingival Index (GI), and Plaque Index (PlI). The models of univariate and logistic regression adjusted for possible confounders were applied for data analysis.

Results: The presence of a CM family history (p=0.000, OR=5.442), deeper Periodontal Pockets (PPD) (p=0.040, OR=1.887), and moderate/severe Gingival Inflammation (GI) (p=0.045, OR=1.542), were statistically significantly associated with the risk of CM developing, compared to healthy individuals, after controlling for smoking, educational and socio-economic status.

Conclusions: The current research suggested positive associations of individuals with CM family history, deeper periodontal pockets, and moderate/severe gingival inflammation, with CM development.

Keywords: Periodontal Disease; Cutaneous Melanoma; Risk Factors; Adults

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Introduction

Melanoma is a type of cancer, typically a cutaneous malignancy, that develops from melanin-producing cells known as melanocytes [1]. It most commonly occurs in the skin but may rarely arise in the mucosal surfaces of the mouth, intestines, or in the eye (uveal melanoma) [1, 2]. In extremely rare cases, melanoma can also occur in the lung, where it is referred to as primary pulmonary melanoma and accounts for approximately 0.01% of all primary lung tumors [3].

Approximately 30% of melanomas arise from pre-existing melanocytic nevi. Changes in a nevus that may indicate malignant transformation include rapid increase in size, irregular borders, variation in color, pruritus, or ulceration [1]. The primary etiological factor in melanoma development is exposure to Ultraviolet (UV) radiation, particularly in individuals with low levels of the skin pigment melanin [2]. UV radiation may originate from the sun or artificial sources, such as tanning devices [2]. Individuals with a high number of nevi, a positive family history of melanoma, or immunodeficiency are at increased risk [1]. Furthermore, rare genetic disorders, such as Xeroderma Pigmentosum, are also associated with a significantly elevated risk [4]. Other risk factors include skin type, e.g., skin that always burns, never tans, presence of benign and atypical

nevi, a personal or family history of melanoma, and obesity [1, 5-7].

Melanoma, is the fifth most common cancer in the U.S., has increased from 8.8/100, 000 in 1975 to 28.42/100,000 in 2022. Cutaneous Melanoma (CM) comprises 94% of cases, with 104,960 U.S. cases projected for 2025 [1]. Despite representing only 1% of skin cancers, CM accounts for over 80% of skin cancer deaths [5]. The age-standardized incidence rate is 3.8/100,000 for males and 3.0/100,000 for females, with cumulative lifetime risks of 0.42% and 0.33%, respectively [8]. An estimated 57,000 people died of CM in 2020, according to GLOBOCAN, leading to age-standardized mortality of 0,7/100,000 for males and 0,4/100,000 for females worldwide [8].

Regarding the prognosis of the disease, according to data from the Surveillance, Epidemiology, and End Results Program, the 5-year relative survival rate for CM has improved substantially over time, increasing from 81.9% in 1975 to 93.3% for individuals diagnosed during the 2011-2017 period. Survival outcomes are strongly stage-dependent at the time of diagnosis, as patients with localized disease (stage I-II) exhibit a 5-year survival rate of approximately 99.4%, which declines to 68.0% for regional disease (stage III) and further to 29.8% for distant metastatic disease (stage IV). Notably, the majority of cases, approximately 83%, are diagnosed at early stages (I-II), whereas only about 4% of cases present at stage IV [1, 5].

CM is divided into several types with different features, such as superficial spreading, amelanotic, desmoplastic, and nodular or polypoid melanoma [1]. Melanoma is often termed “malignant melanoma” in clinical and public contexts. However, the medical consensus emphasizes that all melanomas are inherently malignant, and there is no recognized entity of a “benign melanoma.” Consequently, the use of the qualifier “malignant” is considered redundant, and the preferred terminology is simply melanoma [9]. Periodontal Disease (PD), particularly its severe form, periodontitis, is a chronic inflammatory condition affecting the supporting structures of the teeth. It is primarily driven by bacterial infection of the gingival tissue and the surrounding alveolar bone [10]. As a chronic inflammatory response to pathogenic dental plaque bacteria [11], PD can contribute to systemic inflammation, evidenced by elevated levels of inflammatory biomarkers in the circulation, including Interleukin-6 (IL-6) and C-Reactive Protein (CRP), among affected individuals [12]. According to the Global Burden of Disease (GBD) Study 2019, approximately 1.1 billion cases of severe periodontitis were recorded in 2019, nearly doubling the prevalence observed in 1990 [13]. PD has also been linked to a range of systemic conditions, including Cardiovascular Diseases (CVD) [14], Diabetes Mellitus (DM) [15], Rheumatoid Arthritis [16], and several types of cancer [17-21], potentially due to shared risk factors [15, 18, 21, 22]. Over the past few decades, increasing attention has been directed toward understanding the association between PD and cancer, as evidence suggests that PD may be associated with elevated risks of overall cancer as well as certain site-specific malignancies [22, 23].

Despite many previous studies, findings regarding the association between PD and cancer risk remain inconsistent, even after adjustment for potential confounders such as smoking, educational and Socioeconomic Status (SES). Notably, few previous reports have specifically examined PD as a potential risk factor for CM [24-26]. The mechanisms underlying these associations are not fully elucidated, but several pathways have been proposed. PD may contribute to cancer risk through systemic inflammation mediated by circulating inflammatory factors, direct bacterial invasion into the bloodstream, or host immunosuppression [27, 28]. To date, no prospective or retrospective epidemiological studies have been conducted in Greece to examine the potential relationship between PD indices and CM risk. The current case-control study aims to investigate the association between PD indices and CM development in a sample of Greek adults.

Materials and Methods

Design of the study and sample size estimation

This case-control study included a total of 258 participants ,136 males, 122 females, aged 39-77 years, comprising 86 patients with CM and 172 healthy controls. Sample size was calculated based on CM prevalence using EPI-TOOLS guidelines (https://epitools.ausvet.com.au) [29], assuming a 95% confidence interval and 80% statistical power. Participants were recruited from two medical clinics and a private dental practice between April 2024 and February 2026. All individuals underwent comprehensive oral and dental clinical examinations and completed a structured standardized medical and dental health questionnaire. Periodontal status was assessed according to World Health Organization (WHO) recommendations for age-specific evaluation [30].

Cases and controls eligibility criteria

To be eligible for inclusion, both CM patients and healthy controls must not have received any periodontal treatment, conservative or surgical, within the preceding six months. Additionally, participants should not have been prescribed systemic glucocorticoids, immunosuppressive agents, or systemic antibiotic regimens during the same period. All individuals were required to have more than 15 teeth and exhibit periodontitis ranging from stage I to IV [31].

Exclusion criteria included the presence of systemic diseases or disorders that could affect oral and periodontal health, such as DM, CVD, acute pulmonary diseases, such as Chronic Obstructive Pulmonary Disease, or any malignancies, as these conditions could introduce confounding or bias in secondary associations [32]. Participants were recruited from the same social and professional environment, were residents of the same city, and presented for routine health follow-ups at the selected medical and dental practices. Members of the same family were excluded to avoid genetic clustering. To minimize selection bias, healthy controls were matched to cases based on age, gender and smoking status, which are established risk factors for periodontitis and may act as covariates in statistical analyses [33, 34].

Once a suspicious lesion has been identified and thoroughly documented, biopsy and histopathological evaluation should be performed. Lesion sampling may be achieved through various techniques, including excisional or partial biopsy. Given that the vertical depth of invasion represents one of the most critical prognostic factors in CM, excisional biopsy of the entire lesion with narrow margins is the preferred approach to ensure accurate diagnosis and facilitate optimal treatment planning [35].

Patients with advanced-stage CM currently undergoing medical treatment, including surgical management, immunotherapy, such as immune checkpoint inhibitors (e.g. anti-PD-1), targeted therapy, such as BRAF and MEK inhibitors, radiation therapy, as well as hospitalized patients, were excluded from the study [36].

Prior to periodontal examination, all participants completed a standardized-modified medical questionnaire [32]. Potential

confounding variables considered for adjustment included age, gender, smoking status (active smoker vs. non-smoker), educational and SES, Body Mass Index (BMI), and general medical history, including current medications and the presence of chronic systemic conditions. Age was categorized into four groups, 39-49, 50-59, 60-69, and ≥70 years. SES was classified as ≤1,000 € or >1,000 €/month. Educational level was categorized as elementary or university/college graduate. Smoking status was defined as, never smokers (individuals who smoked <100 cigarettes in their lifetime), former smokers (those who smoked at least 100 cigarettes in their lifetime but reporting that they currently do not smoke), and current smokers (those who smoke at least 100 cigarettes in their lifetime and reporting current daily or occasional smoking). BMI was classified as normal (< 30 kg/m^2) or high (≥ 30 kg/m^2) and considered a risk factor for CM development [6, 7].

To assess intra-examiner reliability, a randomly selected subset of 52 participants (20% of the sample) was re-examined clinically by the same dentist three weeks after the initial examination. No significant differences were observed between the first and second assessments (Cohen's Kappa=0.96). No oral hygiene instructions were provided to participants during this three-week interval.

Periodontal condition evaluation

Periodontal evaluations were conducted in the dental practice using a Williams periodontal probe with controlled force (0.2 N; DB764R, Aesculap AG & Co. KG), a mouth mirror, tissue forceps, and dental light source. Remaining roots and third molars were excluded from scoring.

The periodontal examination focused on the assessment of Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Plaque Index (PlI), and Gingival Index (GI), to evaluate overall periodontal health status. All indices were assessed at four sites per tooth (mesio-lingual, disto-lingual, disto-buccal, and mesio-buccal) across all quadrants. The worst value for each index was recorded to the nearest 1.0mm and coded as dichotomous variables.

PPD was classified as stage I (maximum PPD≤4.0 mm) and stages II-IV (PPD>4.0 mm to≥6.0 mm [31]. CAL severity was categorized as normal/mild: 1.0-2.0 mm of attachment loss, and moderate/severe: ≥3.0 mm of attachment loss [37]. Gingival Inflammation severity (GI) was coded as: score 0: normal gingival tissue or mild inflammation, corresponding to Löe and Silness [38] scores 0-1, and score 1: moderate to severe inflammation, corresponding to Löe and Silness [38] scores 2-3.

The Plaque Index (PlI), according to Silness and Löe [39], was assessed at the same sites using the Williams periodontal probe. Dental plaque was considered present if it was either visually detectable with the naked eye or if there was an accumulation of soft matter within the gingival pocket and/or on the tooth and gingival margin. Scores of 2 and 3 on the PlI were used to indicate plaque presence, and plaque was recorded as present if at least one site per participant exhibited these characteristics [39].

Ethical Consideration

In Greece, formal ethical approval is typically required for experimental studies, such as clinical trials, conducted under the supervision of national health authorities. The current study was designed as a retrospective case-control investigation and, therefore, did not require review or approval by the aforementioned regulatory authorities.

All participants were informed about the aims and procedures of the study and provided written informed consent prior to enrolment.

Results

The mean age of the study sample was 53 ± 4.5 years. The main histological types concerned superficial spreading (88.2%), nodular (7.5%), and amelanotic (4.3%). Table 1 presents the outcomes after application of Univariate analysis, and showed that advanced age (p=0.005), the presence of a CM family history (p=0.000), deeper Periodontal Pockets (PPD) (p=0.034), moderate/severe attachment loss (CAL) (p=0.011), and moderate/sever Gingival Inflammation (GI) (p=0.052) were statistically significantly associated with risk for CM development. Table 1 also displays Unadjusted OR's and 95% CI for each variable analyzed. After application of the first step (step 1a -Enter method) of the logistic regression model it was found that a CM family history (p=0.000) and deeper periodontal pockets (p=0.028) were significantly associated with risk of CM appearance. Table 2 also demonstrates Adjusted OR's and 95% CI for each index examined. The final step (step 7a -Wald method) of the model showed (Table 2) that a CM family history (p=0.000), deeper periodontal pockets (p=0.040), and GI (p=0.045), were statistically significantly associated with risk for developing CM, after adjusting for known confounders.

Discussion

Over the past decades, the association between PD, gingivitis, and especially periodontitis, and cancer risk has been extensively investigated, often yielding conflicting results. As a chronic inflammatory condition, PD has been linked to a wide range of systemic diseases and disorders [40-43]. 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, is associated with an increased risk of several cancers across different populations [22, 44-50]. 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 [51].

After adjustment for confounding factors, individuals with a CM family history, and PD variables such as PPD and GI, were statistically significantly associated with the risk of CM development. On the other hand, common epidemiological indices such as gender, advanced age, SES and educational status, smoking, and elevated BMI were found to be controversial in relation to the risk of developing CM. Recent studies have shown that higher SES, and educational status had an increased association with CM incidence, while smoking was not associated with melanoma-specific mortality, but was appeared to be associated with reduced incidence of melanoma [52, 53]. Regarding BMI, the findings were also controversial, as some articles showed that BMI has been positively associated with CM risk [6, 7], whereas other provided no evidence for a causal association between higher BMI and melanoma [54].

The current report demonstrated that family history significantly increases CM risk, finding that was in accordance with those from previous studies [55-57]. A positive family history of CM is a well-established risk factor that significantly increases the likelihood of developing CM. Familial CM accounts for approximately 10% of all melanoma cases and typically follows an inheritance pattern consistent with pathogenic germline mutations, among which

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	47 (54.7)	89 (51.7)	0.659	1.124 (0.669-1.889)
Females	39 (45.3)	83 (48.3)		
Age			0.005*	-
39-49	10 (11.6)	26 (15.1)		
50-59	38 (44.2)	40 (23.3)		
60-69	21 (24.4)	69 (40.1)		
70+	17 (19.8)	37 (21.5)		
Socio-economic status			0.480	1.207 (0.716-2.032)
Low	49 (57.0)	90 (52.3)		
High	37 (43.0)	82 (47.7)		
Education level			0.597	1.150 (0.685-1.930)
Low	45 (52.3)	84 (48.8)		
High	41 (47.7)	88 (51.2)		
CM family history			0.000*	0.195 (0.111-0.341)
Absence	33 (38.4)	131 (76.2)		
Presence	53 (61.6)	41 (23.8)		
Smoking			0.424	0.807 (0.476-1.366)
Never smokers	34 (39.5)	77 (44.8)		
Previous/current smokers	52 (60.5)	95 (55.2)		
Body Mass Index			0.291	0.756 (0.450-1.271)
<30 kg/m^2	40 (46.5)	92 (53.5)		
≥30 kg/m^2	46 (53.5)	80 (46.5)		
Probing pocket depth			0.034*	0.570 (0.338-0.961)
≤ 4.00 mm	38 (44.2)	100 (58.1)		
≤ 4.00- ≥ 6.0 mm	48 (55.8)	72 (41.9)		
Clinical Attachment Loss			0.011*	1.976 (1.168-3.343)
1.00-2.00 mm	51 (59.3)	73 (42.4)		
≥ 3.0 mm	35 (40.7)	99 (57.6)		
Gingival Index			0.052*	1.676 (0.995-2.823)
Absence/Mild	46 (53.5)	70 (40.7)		
Moderate/Severe	40 (46.5)	102 (59.3)		
Plaque Index			0.595	1.152 (0.683-1.945)
Absence	50 (58.1)	94 (54.7)		
Presence	36 (41.9)	78 (45.3)		

*_p_-value: statistically significant

alterations in CDKN2A are the most extensively characterized. In recent years, additional susceptibility genes including MC1R, MITF, TERT, TERF2IP. CDK4, ACD, POT1, and BAP1, have been implicated in familial CM predisposition. However, accurate prediction of mutation carriage remains challenging due to the complex, polygenic nature of CM susceptibility, which involves multiple low-penetrance alleles, genetic modifiers, and environmental influences [55-57].

PPD serves as a reliable measure for assessing the severity of PD [58], and acts as an indicator of current inflammatory status [59]. Our findings demonstrated a statistically significant association between increased PPD and the risk of developing CM.

In contrast, CAL is a critical index for evaluating cumulative periodontal tissue destruction, reflecting the long-term impact of prior inflammatory episodes. While both PPD and CAL characterize the destructive phases of chronic periodontal inflammation [60], the present results showed no significant association between CAL and CM risk.

GI quantifies the severity of gingival inflammation; however, it is less frequently employed in large-scale epidemiological studies, despite its utility in estimating the localized inflammatory load. Although certain evidence suggests that gingival inflammation may serve as a risk factor for various malignancies [61], other studies have

Table 2: Presentation of association between potentially risk factors and CM according to Enter (first step-1[a]) and Wald (last step 7[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	,210	,304	,477	1	,490	1,234	,680	2,239
	Age	,218	,289	,451	1	,458	,889	,651	1,213
	Socioecon.stat	,049	,313	,025	1	,875	1,051	,569	1,942
	Educ.lev	-,123	,321	,146	1	,702	,885	,472	1,658
	Melan.fam.hist	1,737	,311	31,086	1	,000*	5,678	3,084	10,454
	Cig.smok	1,373	,309	,516	1	,246	1,289	,867	1,693
	Bmi	1,125	,332	,401	1	,305	1,134	,556	1,468
	Prob.pock.depth	,726	,331	4,819	1	,028*	2,066	1,081	3,951
	Clin.att.loss	1,278	,323	1,495	1	,177	1,416	,621	1,783
	Ging.index	1,577	,315	1,360	1	,067	1,561	,673	1,841
	Pl.index	1,193	,308	1,394	1	,530	1,213	,763	2,020
	Constant	2,785	,496	12,506	1	,113	1,456	-	-
Step 7[a]	Melan.fam.hist	1,694	,302	31,450	1	,000*	5,442	3,010	9,838
	Prob.pock.depth	,635	,304	4,219	1	,040*	1,887	1,029	3,458
	Ging.index	1,612	,305	4,029	1	,045*	1,542	,698	1,986
	Constant	2,994	,272	13,350	1	,000	1,370	-	-

[a]Variable(s) entered on step 1: gender, age, socioecon.stat, educ.lev, melan.fam.hist, cig.smok, bmi, prob.pock. depth, clin.att.loss, ging.index, pl.index

failed to establish a definitive association [62, 63].

PlI by Silness and Löe [39] remains the standard for assessing dental plaque accumulation, representing the primary etiological factor for the onset of periodontal inflammatory responses.

In a study by Nwizu *et al*., [25], which utilized structured self-administered and interviewer-administered questionnaires, a statistically significant multivariable-adjusted positive association was recorded between PD and CM [HR=1.23, 95% CI=1.02-1.48]. Notably, the association was more pronounced among never-smokers [HR=1.42, 95% CI=1.08-1.85]. Although the risk for CM development appeared stronger in the never-smoker subgroup compared to the overall study population, the underlying biological mechanisms for this discrepancy remain to be elucidated [25].

Ma *et al*., [64] conducted a meta-analysis of three studies involving 87,139 participants to evaluate the impact of periodontitis on CM risk [24-26]. All included studies adjusted for critical covariates, such as age, educational, and smoking status. The pooled analysis revealed a significant association between periodontitis and CM (HR=1.21, 95% CI=1.03-1.42), with no evidence of heterogeneity (I^2=0%, p=0.70). However, upon the exclusion of the study by Nwizu et al., [24], the overall estimate lost its statistical significance. This shift is likely attributable to the fact that the aforementioned study constituted a substantial proportion of the total sample size. Due to the limited number of available studies, a subgroup analysis could not be carried out.

However, these findings do not provide robust evidence of causality between PD and CM or other cancer types. To date, no systematic meta-analysis has focused on quantifying the risk of CM development in relation to periodontitis [64].

Significant inverse associations were identified between tooth loss and the risk of CM. In contrast, no significant association was established between PD and CM [23].

Another group of investigators observed no such a link, even when limited to never-smokers (HR=1.20, 95% CI=0.89-1.63) [24], while a recent report also found no association between the relationship examined [65].

The biologic mechanisms for the implication of oral health or PD in CM development are not well understood. Several hypotheses have been suggested for the mechanisms resulting in CM occurrence.

Inflammation is a well-established hallmark of cancer [66]. Periodontitis, as a chronic infectious disease, promotes persistent low-grade inflammation, which has been implicated in cancer initiation and progression [67-69]. A potential role for immunoinflammatory processes has been proposed, as inflammation is a shared feature of both periodontitis and carcinogenesis [23].

Periodontal inflammatory disease and calculus have been considered risk factors for neoplasms in humans, as inflammation is considered an enabling hallmark of cancer [66, 70, 71] and can be considered as the underlying cause of the neoplasm.

Chronic inflammation plays a pivotal role in oncogenesis by potentially inhibiting apoptosis [72]. Several mechanisms have been proposed to elucidate the association between PD and malignancy. Periodontitis may serve as a marker of systemic immune dysfunction, reflecting impaired host surveillance of tumor growth and progression [73]. Furthermore, inadequate oral hygiene and PD, often exacerbated by tobacco use and dietary factors, facilitate the formation of endogenous nitrosamines by nitrate-producing bacteria [74-76]. Consequently, tooth loss resulting from poor oral health may further accelerate nitrosamine production [77].

Additional pathogenic pathways include the microbial production of ethanol by-products, such as acetaldehyde [78,79], and the

overproduction of Matrix Metalloproteinases (MMPs). Specifically, MMP-2 and MMP-9 degrade type IV collagen within the epithelial and vascular basement membranes-a process critically linked to tumor cell invasion [80]. Notably, MMP-9 levels are significantly elevated in individuals with periodontitis [81].

Inflammation further promotes carcinogenesis by enhancing cellular proliferation and mutagenesis, reducing adaptation to oxidative stress, promoting angiogenesis, and increasing the secretion of inflammatory mediators, such as cytokines, chemokines, etc. [82]. Moreover, periodontitis is associated with altered antioxidant enzyme activity [83]. The severity of PD is associated with increased Glutathione Peroxidase 1 (GPX1) transcript levels. The resulting oxidative and nitrosative stress from these inflammatory processes generates free radicals (ROS, RNI), potentially inducing DNA mutations or interfering with DNA repair mechanisms [84].

Concerning the association between periodontitis and CM, emerging evidence suggests that the human microbiome, encompassing gut, oral, and skin microbial communities, exerts a substantial influence on both CM pathogenesis and the efficacy of immunotherapy [85-87]. It is hypothesized that periodontitis-induced dysbiosis may disrupt systemic microbial homeostasis, thereby potentially promoting melanoma progression.

Discrepancies between studies could be due to differences in study design, population or periodontal disease measures used. The possible explanation for the conflicting results could be attributed to differences in the study samples in relation to age, gender, SES, educational status concerning smoking habits, and the extent and severity of PD. In most cases the confounding effect of smoking has been taken into account applying multivariate regression models with a non-quantitative smoking variable. In other similar reports the confounding effect of smoking has been removed by excluding smokers. Confounding represents a bias that the investigator hopes to prevent or remove from the effect estimate. In contrast, effect modification is a property of the effect under study. Tobacco and other risk factors, such as age, SES, and educational status can act as confounding factors or effect modifiers [88,89].

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 fuzzy boundaries. This may result in incomplete control for the impact of smoking and bias estimates of an intervening variable like periodontal disease [90,91].

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 family CM history, with deep Periodontal Pockets (PPD), and moderate/severe Gingival Inflammation (GI) were significantly associated with an increased risk of developing CM.

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