Original paper

Evaluation of the association between periodontal disease and total cancer risk: A cross-sectional study

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Abstract

Background. The body is in a continuous state of inflammatory burden due to local and systemic inflammation, which is triggered in periodontal tissues in response to microorganisms. A number of studies have linked periodontitis to systemic diseases such as diabetes mellitus, cardiovascular disease and respiratory disease. Periodontal inflammation acts as a focus of infection, which can cause detrimental effects on distant target organs. In some cases, it may lead to tumor progression in various cancers.

Objectives. The aim of the study was to evaluate the correlation between periodontal disease (PD) and its potential role as a risk factor for the development of systemic cancer and its metastasis.

Material and methods. A single-center, cross-sectional study was conducted, including 66 patients with different systemic malignancies (group 1, the test group) and 66 healthy individuals (group 2, the control group). Group 1 was further subdivided into 2 categories: M0, comprising patients without metastases ($n = 34$); and M1, comprising patients with distant metastases ($n = 32$). The number of missing teeth, Greene and Vermilion's simplified oral hygiene index (OHI-S), probing pocket depth (PPD), Löe and Silness' bleeding on probing (BoP), clinical attachment loss (CAL), and Ramfjord's periodontal disease index (PDI) were recorded. Appropriate statistical tests were performed to analyze the data. A p-value <0.05 was considered statistically significant.

Results. The differences between the PDI, CAL and PPD values in both group 1 and group 2 were found to be statistically significant ($p = 0.000$). In M0 and M1, no statistically significant differences were observed between any of the parameters. The odds ratios (*OR*s) between group 1 and group 2 for CAL and PDI were 3.986 and 4.286, respectively. The *OR*s for M0 and M1 with regard to CAL and the mean number of teeth lost were 0.373 and 0.188, respectively.

Conclusions. The findings of the study indicate a significant association between the overall risk of cancer and PD. In cases of known systemic malignancies, no significant correlation has been identified between PD and the risk of metastasis.

Keywords: periodontitis, metastasis, attachment loss, total cancer risk, periodontal inflammation

Introduction

Cancer, or malignant neoplasm, is characterized by uncontrolled cell growth, tissue invasion and metastasis to various organs via the hematological and lymphatic systems.[1] Inflammation plays a critical role in tumor progression, enhancing cellular proliferation and mutagenesis, among others.[2] As stated in a report by Papapanou et al., "periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilm and characterized by progressive destruction of the tooth-supporting apparatus."[3] This is clinically detectable as periodontal pockets and alveolar bone loss.[3] The inflammatory response to periodontal infection extends beyond the oral cavity and leads to elevated levels of circulating inflammatory markers. Periodontal infection has been linked to various organs and systemic diseases such as cardiovascular disease, diabetes mellitus or adverse pregnancy outcomes.[4]

Chronic diseases, including type 2 diabetes, heart disease, stroke, hypertension, and cancer, can affect morbidity and quality of life of patients. While the majority of these diseases are not life-threatening, cancer is a notable exception, as it requires immediate attention. In a study by Michaud et al., it was found that after adjustment for known risk factors such as smoking and diet, patients with a history of periodontal disease (PD) had an increased risk of overall cancer compared to those without PD.[5] However, there is limited literature on the association between PD and overall cancer risk. The rationale of the study was to assess the potential role of PD as a risk factor for the development of systemic cancer and its metastasis. The aim of the present study was to evaluate the association between PD and overall cancer risk, as well as the risk of cancer metastasis in individuals with systemic malignancies. The novelty of this study lies in its evaluation of the role of periodontitis in the metastasis of cancer, which has not been extensively investigated to date.

Material and methods

This cross-sectional, case–control study has been approved by the ethics committee of Modern Dental College and Research Centre (approval No. IEC/MDCRC/2011-2012/S). The study included 132 individuals, who were divided into 2 groups. Group 1, the test group, consisted of 66 patients with known systemic malignancies, while group 2, the control group, consisted of 66 healthy individuals. Group 1 was further divided into 2 subgroups: M0 (34 patients with no distant metastases); and M1 (32 patients with distant metastases). Both the test and control groups were evaluated for PD.

The inclusion criteria were as follows: patients with systemic malignancies, including ovarian, breast, lung, rectal, cervical, and esophageal cancer; cancer patients who had not undergone more than 1 module of chemotherapy; individuals between the ages of 25 and 70; and family members of cancer patients who were from the same socioeconomic strata and had at least 14 teeth present in the oral cavity. Patients with oral cancer, those who have recently undergone tracheotomy, those who had received more than 1 module of anticancer drugs, as well as individuals with blood cancer (leukemia) and those suffering from other systemic diseases, including diabetes mellitus, hypertension, hypothyroidism, and hyperthyroidism were excluded from the study. The diagnosis of cancer and metastasis was made by experts on the basis of a histopathological report, computerized tomography scans and magnetic resonance imaging scans.

Prior to the commencement of the study, informed consent was obtained from all the patients and their demographic data was recorded. A dichotomous scoring system was employed to record the habit history, including both tobacco chewing and smoking. The periodontal examination consisted of the number of missing teeth, Greene and Vermilion's simplified oral hygiene index (OHI-S), probing pocket depth (PPD), Löe and Silness' bleeding on probing (BoP), clinical attachment loss (CAL), and Ramfjord's periodontal disease index (PDI) on 4 sites of 6 Ramfjord's teeth (14, 11, 16, 36, 31, 44).

Statistical analysis

The data was analyzed using the IBM SPSS Statistics for Windows software, v. 20.0 (IBM Corp., Armonk, USA). The unpaired *t*-test, odds ratio (*OR*), Mann–Whitney *U* test, and multiple regression analysis were applied to obtain the results. A *p*-value of less than 0.05 was considered statistically significant.

Results

The unpaired *t*-test was used to evaluate the difference in means between the test and control groups. No statistically significant differences were observed between the test and control groups with respect to the number of teeth lost, mean age and the OHI-S. The mean PDI was 3.56 ±1.48 for the test group and 2.54 ±1.45 for the control group. The mean PPD was found to be 2.43 ±0.65 mm for the test group and 0.84 ±0.89 mm for the control group. The mean CAL was 3.40 ±2.17 mm and 1.59 ±1.60 mm for the test and control groups, respectively. The difference between these 3 parameters in both groups was found to be statistically highly significant (p = 0.000) (Table 1). The mean difference in age,

Table 1. Clinical parameters of cancer and non-cancer patients

Parameter	Test group ($n = 66$) $M \pm SD$	Control group ($n = 66$) $M \pm SD$	*p*-value
Age [years]	49.00 ±3.73	52.70 ±9.74	0.077
Teeth lost, *n*	2.33 ±4.95	2.38 ±3.39	0.951
OHI-S	3.09 ±1.60	2.78 ±1.25	0.214
PDI	3.56 ±1.48	2.54 ±1.45	0.000**
PPD [mm]	2.43 ±0.65	0.84 ±0.89	0.000**
CAL [mm]	3.40 ±2.17	1.59 ±1.60	0.000**

M – mean; *SD* – standard deviation; OHI-S – simplified oral hygiene index; PDI – periodontal disease index; PPD – probing pocket depth; CAL – clinical attachment loss; ** statistically highly significant ($p < 0.005$, unpaired *t*-test).

Table 2. Clinical parameters of patients with and without metastasis

Parameter	Metastasis patients (M1, $n = 32$) $M \pm SD$	Non-metastasis patients (M0, $n = 34$) $M \pm SD$	*p*-value (unpaired *t*-test)
Age [years]	48.97 ±14.58	49.03 ±13.11	0.986
Teeth lost, *n*	3.12 ±5.46	1.06 ±0.24	0.211
OHI-S	3.20 ±1.57	2.99 ±1.66	0.607
PDI	3.75 ±1.39	3.39 ±1.56	0.313
PPD [mm]	2.56 ±0.64	2.87 ±0.46	0.432
CAL [mm]	3.66 ±2.29	3.17 ±2.07	0.371

the number of teeth lost, as well as the OHI-S, PDI, CAL, and PPD was found to be statistically non-significant between the M0 and M1 groups (Table 2).

The χ^2 test was conducted to assess the differences in habit history (tobacco use) and sex between the test and control groups, as well as between metastasis (M1) and non-metastasis (M0) patients. The analysis revealed a statistically significant difference in sex between the test and control groups ($p = 0.035$) (Table 3).

The Mann–Whitney *U* test was applied to evaluate the mean difference between the test and control groups with respect to the BoP. The difference was found to be statistically significant ($p = 0.019$).

A multiple regression analysis was conducted to ascertain the impact of individual confounding factors. The analysis demonstrated that the total number of teeth lost, CAL, sex, and tobacco use exhibited statistically significant correlations with the incidence of cancer. The adjusted *OR* at the 95% confidence interval (*CI*) was found to be 30.947 and 27.286 for tobacco use and the CAL, respectively (Table 4). The elevated *OR* can be attributed to the smaller sample size of the study.

Table 5 illustrates the *OR*s for the CAL and PDI in group 1 and group 2, which were found to be 3.986 and 4.286, respectively. Additionally, the *OR* for the CAL and the mean number of teeth lost for the M0 and M1 groups was 0.373 and 0.188, respectively.

Table 3. Differences in habit history and sex between the study groups

Group	Habit history (tobacco use)				Sex (male)			
	present	absent	χ^2 value	*p*-value	present	absent	χ^2 value	*p*-value
Test group ($n = 66$)	29 (43.9%)	37 (56.1%)	3.674	0.055	22 (33.3%)	44 (66.7%)	4.466	0.035*
Control group ($n = 66$)	40 (60.6%)	26 (39.4%)			34 (51.5%)	32 (48.5%)		
Metastasis patients (M1, $n = 32$)	17 (53.1%)	15 (46.9%)	0.504	0.478	10 (31.2%)	22 (68.8%)	0.121	0.728
Non-metastasis patients (M0, $n = 34$)	21 (61.8%)	13 (38.2%)			12 (35.3%)	22 (64.7%)		

* statistically significant ($p < 0.05$).

Table 4. Results of the multiple regression analysis for the test and control groups

Variable	B	*SE*	Wald	*df*	*p*-value	Exp(B)/*OR*
Age	–0.089	0.046	3.783	1	0.052	0.914
Sex (male)	–5.038	1.649	9.333	1	0.002**	0.006
Habit history (tobacco use)	3.432	1.541	4.969	1	0.026*	30.947
Number of teeth lost	–0.679	0.184	13.677	1	0.000**	0.507
PPD	1.176	0.88	1.785	1	0.182	3.241
OHI-S	–0.779	0.532	2.142	1	0.143	0.459
BoP	2.176	1.168	3.466	1	0.062	8.815
PDI	–0.198	0.682	0.085	1	0.771	0.823
CAL	3.306	0.882	14.041	1	0.000**	27.286
Constant	1.182	2.186	0.291	1	0.594	3.253

B – estimated coefficient; *SE* – standard error; *df* – degrees of freedom; Exp(B) – exponential value of B; *OR* – odds ratio; BoP – bleeding on probing; * statistically significant ($p < 0.05$); ** statistically highly significant ($p < 0.005$).

Table 5. Odds ratios for the selected variables in the study groups

Parameter		*OR*	95% *CI*	
			lower	upper
CAL (test/control) *n* = 132	CAL (1/2)	3.986	1.808	8.787
	cohort cancer = 1 (≤3 mm)	2.174	1.307	3.616
	cohort cancer = 2 (>3 mm)	0.545	0.397	0.750
PDI (test/control) *n* = 132	PDI (1/2)	4.286	2.069	8.877
	cohort cancer = 1 (≤3 mm)	2.079	1.408	3.070
	cohort cancer = 2 (>3 mm)	0.485	0.331	0.710
CAL (M1/M0) *n* = 66	CAL (1/2)	0.373	0.138	1.011
	cohort metastasis = 1 (≤3 mm)	0.606	0.363	1.013
	cohort metastasis = 2 (>3 mm)	1.624	0.974	2.707
Number of teeth lost (M1/M0) *n* = 66	teeth lost (1/2)	0.188	0.036	0.964
	cohort metastasis = 1 (≤3 mm)	0.536	0.347	0.826
	cohort metastasis = 2 (>3 mm)	2.857	0.810	10.074

CI – confidence interval; 1/2 – analyzed study groups.

Discussion

The present study was conducted to establish the association between PD and cancer and to further substantiate the relationship between periodontitis and its systemic effects. The mean age and socioeconomic strata of the test and control groups were similar, minimizing the confounding effect of age, genetics, environmental factors, and socioeconomic status. The present study excluded patients with oral cancer because of the difficulty in establishing whether PD was the cause or effect of oral cancer, given the poor and compromised oral hygiene often observed in these patients. The inclusion of oral cancer patients could have led to a biased approach and affected the overall results in a significant manner, potentially leading to a type I error.

The effect of tobacco was nullified in both the test and control groups, as evidenced by a non-significant difference. An earlier study had estimated that the risk of lung cancer increases by 20-fold in smokers compared to non-smokers.[6] In our study, all types of systemic cancers were included, suggesting that concerns about residual confounding by smoking may not be applicable to all cancers.

The present study revealed that the mean number of teeth lost was statistically similar in both cancer and non-cancer patients. Tu et al. reported no significant increase in the risk of cancer-related mortality with increased number of missing teeth.[7] They considered the association between lung cancer and tooth loss to be evidence of residual confounding due to smoking.[7] Cabrera et al. also found no significant association between cancer-related mortality and an increased number of missing teeth.[8] Michaud et al. did not find any association between esophageal cancer and PD, which was verified by radiographic bone loss or missing teeth.[5] This is in contrast to the study conducted by Abnet et al., who reported a stronger association between tooth loss and upper gastrointestinal (GI) cancer, which might be attributed to changes in dietary habits.[9] They also reported age as an effect modifier, with the greatest increase in risk observed among participants under 50 years of age.[9] Watabe et al. observed a significant dose–response relationship between the odds of developing gastric cancer and the number of teeth lost.[10] In a large-scale case–control study including 5,240 cancer patients, the association between tooth loss and 14 common cancers was evaluated. After adjusting for potential confounding factors, a significant positive association was observed between tooth loss and an increased risk of head and neck, esophageal, and lung cancers.[11] It was therefore proposed that the preservation of teeth may decrease the risk of these cancers.[11] Shi et al. performed a dose–response meta-analysis, including 25 studies, to clarify and quantify the correlation between tooth loss and the risk of cancer.[12] They concluded that with each additional 10 teeth lost, there was a 9% increment in cancer risk. They also estimated a 3–31% increase in the risk of various cancers, including head and neck, esophageal, gastric, colorectal, pancreatic, lung, hematopoietic and bladder cancers, with tooth loss in a dose–response manner.[12] The dissimilarities in these results can be attributed to the variation in the consideration of the cause of tooth loss in the abovementioned studies. In most of the aforementioned studies, the reasons for tooth loss were not taken into consideration and were largely self-reported. Similarly, in our study, we had to rely on the information provided by patients regarding the cause of tooth loss.

In the present study, no statistically significant difference was identified in the OHI-S between the test group and the control group. This study included patients who had not undergone more than 1 module of chemotherapy because, in such patients, the effect of chemotherapeutic drugs on periodontal health, quality of life and dexterity might not have been considered. Additionally, factors with a substantial impact on oral hygiene, such as age, socioeconomic background and tobacco history, were comparable between the groups. In another study, a significant correlation was demonstrated between an increased risk of esophageal cancer and poor oral hygiene, as well as an increased number of tooth loss (in patients controlled for smoking).[13]

Demirer et al. found that patients with stomach cancer brushed their teeth less often and had a higher prevalence of deficient teeth compared to controls.[14]

Statistically significant differences were identified between cancer patients and healthy subjects with respect to the PDI, PPD and CAL. Two studies evaluated periodontal health using Russell's periodontal index and self-reported history of PD, which was validated by radiographic examination.[5,15] Both studies found an increased risk of overall cancer-related mortality in patients with periodontitis.[5,15] In the present study, the *OR* was 4.286 for PDI, whereas in other studies, the *OR* was reported to be 1.14[5] and 1.55.[15]

In a retrospective study by Chung and Chan, the evidence of an association between all-cause, all-cancer and specific-cancer mortality related to lung and prostate cancer and PD was inconclusive.[16] Ding et al. conducted an inverse-variance weighted Mendelian randomization analysis and did not establish any significant causal relationship between breast cancer and periodontitis.[17] Meurman et al. performed a 30-year follow-up for the investigation into the association between periodontal inflammation (PI), including gingivitis and periodontitis, and all types of malignancies.[18] The authors reported that the probability of developing cancer increased by approx. 38% in periodontitis patients, whereas no association was identified in those with gingivitis.[18] Cheng et al. proposed that interleukin (IL)-1β plays a role in breast cancer and its metastatic progression.[19] It was hypothesized that PI promotes metastasis of breast cancer by recruiting myeloid-derived suppressor cells (MDSCs). Pyroptosis-induced IL-1β generation was detected in patients with PI, which resulted in the downstream signaling of monocyte chemoattractant protein-1 (CCL2), chemokine ligand 5 (CCL5) and C-X-C motif chemokine 5 (CXCL5). This caused the formation of pre-metastatic niches within the inflammatory site during the initial stages of metastasis. The authors thus emphasized the necessity of controlling PI.[19] Hwang et al. evaluated the impact of PD treatment in a cohort of 38,902 patients and subsequent cancer risk.[20] They concluded that PD treatment resulted in a significant reduction in overall cancer risk, with the greatest impact observed in patients with GI, lung, gynecological, and brain malignancies.[20] As the present study is a non-interventional study, the effects of periodontal therapy on inflammation, cancer and metastasis could not be assessed.

A meta-analysis conducted by Verma et al., which included 194,850 participants from observational studies, concluded that there is an increased risk of lung cancer occurrence in patients with chronic periodontitis, with a risk ratio of 1.41 for lung neoplasm.[21] Similar findings were reported by Kesharani et al. in a pooled analysis of 12 studies, after controlling for age and smoking.[22] The researchers observed that the incidence of lung cancer was twice as high in PD patients and proposed that periodontitis may be a potential risk factor for the development of lung cancer.[22] A meta-analysis by Ma et al. revealed a potential link between periodontitis and various cancers, including esophageal, prostate, hematological, and melanoma of the skin.[23] However, a recent meta-analysis by Corbella et al. did not establish any considerable correlation between periodontitis and cancer.[24]

A comparative analysis of cancer patients with and without metastasis revealed no statistically significant differences in any of the examined parameters. These findings can be attributed to the small sample size (M0 = 34, M1 = 32). Patients with cancer and a CAL of more than 3 mm exhibited a 1.624-fold increased risk of developing metastasis, while those with a greater number of missing teeth demonstrated a 2.857-fold elevated risk of metastasis. To the best of our knowledge, no studies have compared the periodontal status of metastatic and non-metastatic groups.

A number of potential mechanisms may account for the observed correlation between PD and systemic cancer (Fig. 1).

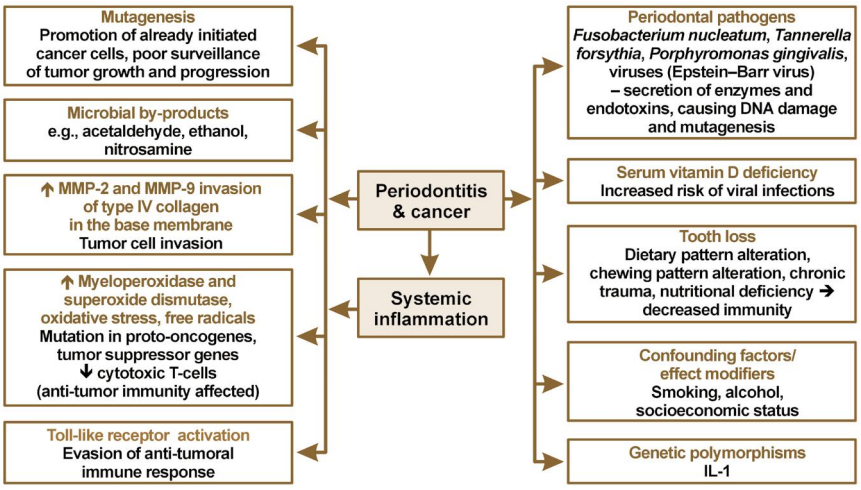

Fig. 1. Proposed pathogenic mechanisms explaining the correlation between periodontal disease and systemic cancer
MMP – matrix metalloproteinase; IL – interleukin.

Inflammation plays an important role in the pathophysiology of both PD and cancer. Chronic inflammation induced by periodontal pathogens may serve to promote and initiate cells, leading to a breakdown of normal growth and the potential promotion of carcinogenesis.[25] Chronic inflammation may also prevent apoptosis.[26] The following are the possible mechanisms explaining the correlation between PD and cancer:

– chronic inflammation may be a sign of poor surveillance of tumor growth by the body.[27] Periodontitis may act as a marker of immune dysfunction, which has implications for tumor growth and progression;
– formation of endogenous nitrosamine by the nitrate-producing bacteria is promoted by inadequate oral hygiene, PD, tobacco, and dietary factors.[28–30] Tooth loss resulting from poor oral hygiene may contribute to greater nitrosamine production[31];
– increased production of ethanol by-products, such as acetaldehyde, by oral microbes[32,33];
– matrix metalloproteinase (MMP)-2 and MMP-9 cleave type IV collagen of epithelium and vascular basement membranes. There is compelling evidence to support the role of MMPs that degrade type IV collagen in tumor cell invasion.[34] It has been demonstrated that MMP-9 levels are elevated in periodontitis subjects[35];
– inflammation may enhance cellular proliferation, mutagenesis, reduce adaptation to oxidative stress, promote angiogenesis, inhibit apoptosis, and increase secretion of inflammatory mediators.[36] All these factors may promote carcinogenesis;
– the enzymatic activity of antioxidant enzymes is reduced in periodontitis.[37] Myeloperoxidase and superoxide dismutase help to regulate inflammation and have been observed to be elevated in periodontitis. A polymorphism in the genes encoding these enzymes has been found to be associated with an increased risk of pancreatic cancer.[38] In a study, the level of glutathione peroxidase 1 (GPX1) transcript levels increased with the severity of PD. Its activity in the salivary and gingival crevicular fluid (GCF) proteome is affected by oxidative stress related to the inflammatory changes observed in PD[37];
– the inflammatory processes generate free radicals and active intermediates, which cause oxidative or nitrosative stress. This may lead to DNA mutations in cells or interfere with DNA repair mechanisms[39];
– serum 25-hydroxyvitamin D has been demonstrated to reduce the risk of PD and tooth loss with cancer by inducing human cathelicidin and LL-37. This reduces the risk of several cancers by lowering the risk of viral infections, such as the Epstein–Barr virus.[40]

The vast majority of cancers are the result of abnormalities in the genetic material of the transformed cells. These abnormalities can be caused by carcinogens such as tobacco, radiation, chemicals, or infectious agents.[25] As viruses are implicated in the etiology of PD, this can indirectly link to the etiology of cancer.[41] The enzymes, metabolic by-products and endotoxins secreted by oral bacteria are toxic to human tissues, causing direct DNA damage to neighboring epithelial cells. They can induce mutations in proto-oncogenes and tumor suppressor genes or interfere with the molecular pathways of cell proliferation or survival.[42]

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 alcohol intake, age and socioeconomic factors, can act as confounding factors or effect modifiers.[9,25] The possible association between PD and lung cancer may be confounded. Periodontitis serves as a surrogate for the unmeasured aspects of smoking and mimics the effects of smoking.[25] Thus, effect modification is a finding that should be reported, rather than a bias to be avoided.[43]

Various mechanisms may explain the relationship between tooth loss and the causation of cancer:

– chronic trauma and irritation of the oral mucosa may play a role in carcinogenesis[10];
– tooth loss is a marker of poor general health and a risk factor[44];
– loss of teeth leads to alterations in dietary patterns, which can elevate the risk of cancer[44];
– tooth loss reduces chewing and affects swallowing, which can contribute to esophageal cancer by causing irritation or damage to the esophageal epithelium[44];
– tooth loss can increase the risk of upper GI cancer through alterations in oral bacterial flora, leading to increased exposure and in vivo production of nitrosamines.[44]

Increased consumption of fruits, vegetables and vitamin C may reduce the risk of oral and gastric cancers. A reduction in fruit and vegetable intake may result from tooth loss.[45]

Genetic factors may increase susceptibility to PD and cancer or may modify the relationship between environmental factors. Genetic polymorphism in IL-1 has been associated with an increased risk of gastric cancer and PD.[46,47] Indirectly, this association may strengthen or facilitate the link between PD and cancer.

Toll-like receptor-5 (TLR-5) is activated by oral bacteria, which results in the evasion of an anti-tumor immune response.[48]

Periodontal pathogens (*Fusobacterium nucleatum*, *Tannerella forsythia*, *Porphyromonas gingivalis*) have been isolated from various cancer lesions. These pathogens modulate the anti-tumor myeloid cell immune system, attract tumor-infiltrating myeloid cells, and create a pro-inflammatory milieu that promotes carcinogenesis.[48]

The epithelial–mesenchymal transition (EMT) barrier can be breached by EMT-predisposing factors like

cytokines and bacterial products. A correlation has been observed between the severity of periodontitis and the expression of the EMT process markers (transforming growth factor-beta 1 (TGF-β1) and vimentin).[49] This suggests that EMT plays an important role in inflammation and cancer metastasis.

Limitations

A key limitation of the current study is its focus on the overall risk of cancer, rather than on specific cancer types. Though nearly all the patients belonged to a lower socioeconomic background, it was not possible to control for other confounding factors, such as malnutrition. Tobacco chewing and smoking were grouped together as habit history, precluding the assessment of the separate outcomes of each behavior.

Conclusions

Although it is not possible to establish a cause-and-effect relationship between PD and the occurrence and metastasis of systemic malignancies using a cross-sectional study design, the findings of this study indicate a significant association between total cancer risk and PD. This study also demonstrates a two-way relationship between PD and the overall risk of cancer. However, no significant association has been identified between PD and the risk of metastasis in known systemic malignancies. Therefore, long-term longitudinal studies with a larger sample size are necessary to establish PD as a risk factor for the occurrence and spread of cancers.

Ethics approval and consent to participate

The study was approved by the ethics committee of Modern Dental College and Research Centre (approval No. IEC/MDCRC/2011-2012/S)

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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