Evaluation of cancer risk in patients with periodontal diseases

Deniz Can GÜVEN1,*, Ömer DİZDAR2, Abdullah Cevdet AKMAN3, Ezel BERKER3, Emre YEKEDÜZ4, Furkan CEYLAN5, Batuhan BAŞPINAR5, İlşın AKBIYIK5, Burak Yasin AKTAŞ1, Deniz YÜCE2, Mustafa ERMAN2, Mutlu HAYRAN2

1. Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey
2. Department of Preventive Oncology, Hacettepe University Cancer Institute, Ankara, Turkey
3. Department of Periodontology, Faculty of Dentistry, Hacettepe University, Ankara, Turkey
4. Department of Medical Oncology, Faculty of Medicine, Ankara University, Ankara, Turkey
5. Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey

* Correspondence: denizcguven@hotmail.com

1. Introduction

Periodontal diseases are polymicrobial chronic inflammatory diseases that cause the damage of the periodontal ligaments and collapse of the adjacent alveolar bone. Periodontal diseases have many stages ranging from mild and short-lived gingivitis to severe periodontitis, which develops after persistent inflammation [1]. The worldwide prevalence of periodontal disease can be up to 90% and gingivitis affects almost half of the adult population [2].

It is thought that periodontal diseases may cause local inflammation as well as important systemic diseases in distant organs including cancers. Proposed mechanisms for this association include the bacteremia secondary to the weakened periodontal epithelium and systemic immune dysregulation [3,4]. The dysbiotic microenvironment in periodontal diseases is stated to create both an immune-evasive and a proinflammatory state, which is required for its persistence [3]. The role of systemic inflammation in increased cancer risk was supported by multiple human studies by the demonstration of increased circulatory cytokines and chemokines in periodontal diseases [5,6].

Several epidemiologic studies have shown that periodontal diseases are associated with an increased risk of cancers including, but not limited to, breast, lung, prostate, and hematological cancers [7–10]. However, assessment methods for periodontal disease in large epidemiological studies were heterogeneous as most studies utilized self-reported data [11] or administrative data [12] rather than examination by a periodontist. We previously showed that moderate to severe periodontitis diagnosed by a periodontist was associated with a 77% increase in cancer risk [13]. This high risk prompted us to further investigate cancer risk in a larger population of...
patients with any periodontal disease, including milder forms of periodontitis, gingivitis, etc. We performed this study to examine cancer risk in a large cohort of over 5000 patients with periodontal disease in comparison with the data of the Turkish National Cancer Registry (TNCR) in the same age and sex groups [14].

2. Materials and methods

2.1. Patients

This study was performed in the Hacettepe University Dentistry and Oncology Hospitals in Ankara, Turkey. Patients diagnosed with any periodontal disease in the Hacettepe University Oral Diagnosis Department and referred to the Periodontology Department between 2007 and 2012 were identified from the hospital registry. Data on the diagnosis of any cancer after periodontal disease were collected from patient files and oncology registries where available. Patients younger than 50 years of age and those with a prior cancer diagnosis were excluded. TNCR 2013 data were used for comparison of age- and sex-specific incidence rates.

The patients were diagnosed using standard clinical and radiographic parameters in accordance with the Periodontal Disease Classification System of the American Academy of Periodontology [15].

The study was approved by the Ethics Committee of Hacettepe University on 24.08.2017 with approval number 17/708.

2.2. Statistical analysis

Standardized incidence rates were calculated after adjustment for age and sex and compared with age and sex-specific incidence rates (SIRs) abstracted from the 2013 TNCR data [14]. The observed number of cases is based on the number of individuals diagnosed with cancer upon follow-up after the diagnosis of periodontal disease. Expected cases represent the total number of patients that would have been reported to the cancer registry within the same period of follow-up as per the TNCR rates under the null hypothesis of no increased risk, given the age and sex structure. The SIR and the 95% confidence interval (CI) for the SIR were calculated using OpenEpi version 3.01 software. A ratio greater than 1.00 indicates that there were more cases observed than expected. P < 0.05 was considered statistically significant.

3. Results

A total of 5199 patients with periodontal disease were included in the study. The median age was 57.7 years and 59% of the patients were female. Median follow-up was calculated as 7.2 years. Three hundred and nineteen new cancer cases were observed in follow-up. The most common cancers were breast cancer (67 of 153 cases) in women and prostate cancer (40 of 166 cases) in men.

The SIRs with 95% CIs are shown in Table 1. Patients with periodontal disease had 17% increased cancer risk (SIR: 1.17, 95% CI: 1.04–1.30, P = 0.006) compared to TNCR data for similar age and sex groups. The overall increased cancer risk did not reach statistical significance in men (SIR: 1.11, 95% CI: 0.95–1.28, P = 0.20), while in women with periodontal disease increased cancer risk was statistically significant (SIR: 1.24, 95% CI: 1.05–1.45, P = 0.008).

In women with periodontal disease, breast cancer (SIR: 2.19, 95% CI: 1.71–2.77, P < 0.001) and head and neck cancer risks (SIR: 4.71, 95% CI: 2.19–8.93, P < 0.001) were significantly increased. In males, prostate cancer (SIR: 1.84, 95% CI: 1.34–2.49, P < 0.001), head and neck cancer (SIR: 3.55, 95% CI 1.87–6.17, P < 0.001), and hematological cancer risks (SIR: 1.76, 95% CI: 0.97–2.93, P = 0.039) were found to be higher than the general population data of similar age and sex groups (Table 1).

4. Discussion

In this study, we showed that the presence of any periodontal disease increased the risk of cancer by 17% in patients from a comprehensive dentistry hospital. The association was particularly significant for breast and head and neck cancer in women and prostate, head and neck, and hematological cancers in men. These findings are in accordance with the findings obtained in our previous study [13] and showed that in a population of patients with milder forms of periodontal disease, cancer risk is still increased, but the magnitude of the risk is lower than the risk for those with moderate to severe periodontitis (Table 2).

A number of underlying mechanisms were proposed for the association between periodontal disease and cancer. These include systemic inflammation induced by the periodontal disease, immune dysregulation, and alteration of the oral flora [16–18]. Periodontitis was proposed to be associated with subclinical systemic inflammation [3,19]. Similar associations have been known for various chronic inflammatory disorders such as inflammatory bowel disease and colorectal cancer [3]. The increase in systemic markers of inflammation such as C-reactive protein, interleukin 6, and tumor necrosis factor-α in the plasma of periodontitis patients supports this association [5,6]. Increased levels of myeloperoxidase and superoxide dismutase, which are among the main regulators of inflammation, were found in periodontitis [20]. An increased gastric cancer risk due to increased inflammation in periodontitis was also proposed [21]. These findings led to the notion that immediate treatment of periodontal disease may reduce the inflammation and its remote effects on other organs [19]. Although mechanisms are unclear, periodontal disease treatment
reduced the subsequent cancer risk by 28% in one study [22], which may be partly explained by a reduction in inflammation.

The highly vascular and fragile structure of the gingival tissue makes it a vulnerable entry site for oral pathogens during daily activities like eating and tooth brushing [6]. Carcinogenic byproducts of oral bacteria metabolism are suggested to be important in the link between periodontal disease and cancer [19]. For example, increased salivary acetaldehyde levels in poor dental health have been shown [23] and may be related to the mediation of oral microbiome contributions to cancer risk in periodontal disease. Oral microbiome changes have been reported in oral cavity cancers [24] and may be related to increased head and neck cancer risk in periodontitis patients. Periodontal pathogens also seem to play roles in the

| Table 1. Standardized incidence ratios (SIRs) with 95% confidence intervals for all and specific cancers in patients with periodontal disease. |
| All | 5199 | 319 | 273.8 | 1.17 | 1.04–1.30 | 0.006 |
| Male total | 2151 | 166 | 150.2 | 1.11 | 0.95–1.28 | 0.197 |
| Male prostate | 40 | 21.7 | 1.84 | 1.34–2.49 | <0.001 |
| Male lung | 23 | 38.3 | 0.6 | 0.39–0.89 | 0.013 |
| Male head and neck | 11 | 3.1 | 3.55 | 1.87–6.17 | <0.001 |
| Male hematologic | 13 | 7.4 | 1.76 | 0.97–2.93 | 0.039 |
| Male colorectal | 14 | 14.2 | 0.99 | 0.56–1.62 | 0.957 |
| Male bladder | 13 | 12.3 | 1.06 | 0.59–1.77 | 0.842 |
| Male stomach | 7 | 9.2 | 0.76 | 0.33–1.50 | 0.468 |
| Male pancreas | 4 | 2 | 2 | 0.64–4.82 | 0.157 |
| Female total | 3048 | 153 | 123.6 | 1.24 | 1.05–1.45 | 0.008 |
| Female breast | 67 | 30.6 | 2.19 | 1.71–2.77 | <0.001 |
| Female lung | 9 | 7.9 | 1.14 | 0.56–2.10 | 0.695 |
| Female head and neck | 8 | 1.7 | 4.71 | 2.19–8.93 | <0.001 |
| Female hematologic | 8 | 7.4 | 1.08 | 0.5–2.05 | 0.825 |
| Female colorectal | 8 | 11.2 | 0.71 | 0.33–1.36 | 0.339 |
| Female bladder | 5 | 2.1 | 1.43 | 0.36–3.90 | 0.535 |
| Female stomach | 1 | 4 | 0.25 | 0.01–1.23 | 0.134 |
| Female pancreas | 3 | 2.8 | 1.07 | 0.27–2.92 | 0.905 |

| Table 2. Comparison of standardized incidence ratios (SIR) with 95% confidence intervals for all and specific cancers in our two studies. |
| Patient population | Any periodontal disease (current study) SIR (95% CI) | Moderate-severe periodontitis [13] SIR (95% CI) |
| All | 1.17 (1.04–1.3) | 1.77 (1.17–2.58) |
| Male total | 1.11 (0.95–1.28) | 1.69 (0.92–2.89) |
| Male prostate | 1.84 (1.34–2.49) | 3.75 (0.95–10.21) |
| Male hematological | 1.76 (0.97–2.93) | 6.97 (1.77–18.98) |
| Female total | 1.24 (1.05–1.45) | 1.84 (1.02–3.07) |
| Female breast | 2.19 (1.71–2.77) | 2.40 (0.88–5.33) |
| N | 5199 | 280 |
was increased by 84% in our study and this finding may
magnitudes (81% vs. 14%) [7,29]. Prostate cancer risk
with periodontitis but with rather different
analyses [9]. Hujoel and Lee reported increased prostate
cancer in a male health professionals cohort
and prostate cancer in a male health professionals cohort
et al. reported an inverse association between tooth loss
and prostate cancer with periodontal disease. Michaud
stratification in our study.

Numerous wide-scale epidemiological studies reported
the association between periodontal disease and cancer
risk. Periodontal diseases were found to be associated
with a 14% increased cancer risk in the WHI cohort [10].
A cohort study from Taiwan that included more than
40,000 patients with chronic periodontitis showed a 23%
increase in total cancer risk compared with age-matched
controls in 5-year follow-up. A lower 5-year cancer-free
survival in the chronic periodontitis cohort was also an
interesting finding indicating a prognostic role of chronic
periodontitis in cancer [28]. In a study by Michaud et al.,
a 13% increased risk of total cancer was observed among
males who never smoked with periodontal disease. In this
study, only smoking-related cancers appeared to increase.
This finding suggested that alterations of immune
pathways may play an important role in the mediation
of periodontal disease and cancer association, giving the
effects of smoking on altered immune response [8].

Breast cancer risk was increased more than twofold in
patients with periodontal disease in this study, similar to
our previous study but somewhat higher than in previous
studies in the literature. In a study by Freudenhelm et
al., in the WHI cohort, 73,737 women were followed for
6.7 years and the presence of periodontal disease was
associated with 14% increased breast cancer risk [11].
Similarly, in a study from Taiwan, chronic periodontitis
was associated with 23% increased breast cancer risk
[28]. In the NHANES I follow-up study, the presence of
periodontitis was associated with a 32% increased risk of
breast cancer but gingivitis did not show an increased risk
[29]. In a study by Söber et al., the presence of any missing
molars in the mandible was associated with increased
breast cancer risk (odds ratio (OR) of 2.36) [30]. The latter
two studies also showed higher risks of cancer in patients
with more advanced periodontal disease resulting in
tooth loss. Our lack of radiological data precluded such a
stratification in our study.

There are conflicting data in the literature on the link
between prostate cancer and periodontal disease. Michaud
et al. reported an inverse association between tooth loss
and prostate cancer in a male health professionals cohort
but did not include nonaggressive prostate cancer in the
analyses [9]. Hujoel and Lee reported increased prostate
cancer risks with periodontitis but with rather different
magnitudes (81% vs. 14%) [7,29]. Prostate cancer risk
was increased by 84% in our study and this finding may
be partly explained by our inclusion of all prostate cancer
cases in the analyses. Differences in the gut microbiome of
prostate cancer patients and patients with benign prostatic
conditions were reported [31]. Estemalik et al. showed
oral pathogens in patients with chronic prostatitis and
benign prostatic hyperplasia [32]. These findings indicate
a possible association between the oral microbiome and
prostate diseases, but comments on driver or bystander
effects could not be made without further data [33].

Periodontal diseases are consistently associated with an
increased risk of head and neck cancers, not surprisingly
when considering the role of microbiome changes and
chronic inflammation in both conditions [19]. Like
periodontal diseases, tooth loss alone was also associated
with head and neck cancer risk [34]. In a metaanalysis of
studies published before March 2013, periodontal disease
was associated with an OR of 2.63 for head and neck
cancers. Although smoking and alcohol are among the
most common risk factors for both periodontal disease
and head and neck cancer, in the studies covaried for
smoking and alcohol, periodontal disease still remained
an independent risk factor with an OR of 2.23 [35]. Our
findings are consistent with the previous literature and
showed a 3- to 4-fold increased cancer risk in both males
and females in a heterogeneous population of patients
with various periodontal diseases.

There are limited data on the literature regarding
the link between hematological cancers and periodontal
disease. Michaud et al. reported a 30% increase in
hematological cancer risk in periodontal disease in a study
of male health professionals [9]. In the Health Professionals
Follow-Up Study, periodontal disease was associated
with increased non-Hodgkin lymphoma and chronic
lymphocytic leukemia/small lymphocytic lymphoma
risks [36]. Hiraki et al. reported no significant association
with periodontal disease and hematological cancers [37].
Hematological cancers were increased in males in both of
our studies, but due to the low number of cases, SIR values
for hematological cancer subtypes were not calculated.

The link between lung cancer and periodontal disease
was investigated several times in the literature [9,37–39].
After adjustment for smoking, some studies did not
find an independent association between periodontal
diseases and lung cancer [29,38], which may be due to
overadjustment in regard to healthy behavior patterns.
There was an inverse association between periodontal
disease and lung cancer in men, which was an unexpected
finding. Due to lack of adjustment for smoking in our
study, we think that underreporting may be the main
reason for the less frequent occurrence of lung cancer in
men with periodontal disease.

Strengths of our study include the relatively large
sample size and diagnosis of periodontal disease by an
experienced team. Confirmation of cancer diagnoses from
the pathology reports rather than administrative data was
important for the reliability of results. However, our study is subject to a number of limitations. First of all, cancer data were taken from patients’ files and hospital records; thus, cancers diagnosed in other centers may have been underreported, altering the results biased towards the null. In addition, the severity and generality of periodontal disease were not evaluated. This prevented us from making further comments on the association of specific periodontal disease parameters and cancer risk. Another limitation was the inability to perform adjustments for factors such as smoking, socioeconomic status, diet, and comorbidities due to lack of data for most patients. The absence of family histories may also be considered among limitations due to possible shared susceptibility driving both conditions, although this shared risk is most evident in the aggressive periodontitis that occurs in early ages [40]. Our study only included patients older than 50 years, which lessens the possibility of confounding due to genetic susceptibility.

Routine clinical applications regarding periodontal disease and cancer risk have yet to be defined. Periodontal disease per se might have a role in carcinogenesis or it might simply be a consequence of an unhealthy lifestyle and habits [41]. Prospective studies with long-term follow-up may aid in discrimination in the future.

In conclusion, these data suggest that chronic inflammatory periodontal diseases are not only a health problem that affects the oral cavity but also has the potential to increase the risk of cancer in local and remote organs by microbiological and immunological mechanisms. Besides other well-known health benefits, maintaining oral/dental health should also be considered and employed as a cancer prevention measure.

References
1. Lauritano D, Sbordone L, Nardone M, Iapichino A, Scapoli L et al. Focus on periodontal disease and colorectal carcinoma. ORAL & Implantology 2017; 10 (3): 229-233. doi: 10.11138/orl/2017.10.3.229
2. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005; 366 (9499): 1809-1820. doi: 10.1016/s0140-6736(05)67728-8
3. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nature Reviews Immunology 2015; 15 (1): 30-44. doi: 10.1038/nri3785
4. Mai X, Genco RJ, LaMonte MJ, Hovey KM, Freudenheim JL et al. Periodontal pathogens and risk of incident cancer in postmenopausal females: the Buffalo OsteoPerio Study. Journal of Periodontology 2016; 87 (3): 257-267. doi: 10.1902/jop.2015.150433
5. Loos BG. Systemic markers of inflammation in periodontitis. Journal of Periodontology 2005; 76 (Suppl. 11): 2106-2115. doi: 10.1902/jop.2005.76.11-S.2106
6. Kim J, Amar S. Periodontal disease and systemic conditions: a bidirectional relationship. Odontology 2006; 94 (1): 10-21. doi: 10.1007/s10266-006-0060-6
7. Lee JH, Kweon HH, Choi JK, Kim YT, Choi SH. Association between periodontal disease and prostate cancer: results of a 12-year longitudinal cohort study in South Korea. Journal of Cancer 2017; 8 (15): 2959-2965. doi: 10.7150/jca.20532
8. Michaud DS, Kelsey KT, Papathanasiou E, Genco CA, Giovannucci E. Periodontal disease and risk of all cancers among male never smokers: an updated analysis of the Health Professionals Follow-up Study. Annals of Oncology 2016; 27 (5): 941-947. doi: 10.1093/annonc/mdw028
9. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K. Periodontal disease, tooth loss and cancer risk in a prospective study of male health professionals. Lancet Oncology 2008; 9 (6): 550-558. doi: 10.1016/S1470-2045(08)70106-2
10. Nwizu NN, Marshall JR, Moysich K, Genco RJ, Hovey KM et al. Periodontal disease and incident cancer risk among postmenopausal women: results from the Women’s Health Initiative Observational Cohort. Cancer Epidemiology, Biomarkers & Prevention 2017; 26 (8): 1255-1265. doi: 10.1158/1055-9965.epi-17-0212
11. Freudenheim JL, Genco RJ, LaMonte MJ, Millen AE, Hovey KM et al. Periodontal disease and breast cancer: prospective cohort study of postmenopausal women. Cancer Epidemiology, Biomarkers & Prevention 2016; 25 (1): 43-50. doi: 10.1158/1055-9965.EPI-15-0750
12. Wen BW, Tsai CS, Lin CL, Chang YJ, Lee CF et al. Cancer risk among gingivitis and periodontitis patients: a nationwide cohort study. QJM 2014; 107 (4): 283-290. doi: 10.1093/qjmed/hct248
13. Dizdar O, Hayran M, Guven DC, Yilmaz TB, Taheri S et al. Increased cancer risk in patients with periodontitis. Current Medical Research and Opinion 2017; 33 (12): 2195-2200. doi: 10.1080/03007995.2017.1354829
14. Ministry of Health. Cancer Statistics of Turkey. Ankara, Turkey: Ministry of Health; 2013.
15. Wiebe CB, Puttnins EE. The periodontal disease classification system of the American Academy of Periodontology—an update. Journal of the Canadian Dental Association 2000; 66 (11): 594-597.
16. Hayashi C, Gudino CV, Gibson FC, Genco CA. Pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specific innate immune inflammatory pathways. Molecular Oral Microbiology 2010; 25 (5): 305-316. doi: 10.1111/j.2041-1014.2010.00582.x
17. Schmidt J, Jentsch H, Stingu CS, Sack U. General immune status and oral microbiology in patients with different forms of periodontitis and healthy control subjects. PLoS One 2014; 9 (10): e109187. doi: 10.1371/journal.pone.0109187
GÜVEN et al. / Turk J Med Sci

18. Garrett WS. Cancer and the microbiota. Science 2015; 348 (6230): 80-86. doi: 10.1126/science.aaa4972

19. Fitzpatrick SG, Katz J. The association between periodontal disease and cancer: a review of the literature. Journal of Dentistry. 2010; 38 (2): 83-95. doi: 10.1016/j.jdent.2009.10.007

20. Wheatley-Price P, Asomaning K, Reid A, Zhai R, Su L et al. Periodontal disease with treatment reduces subsequent cancer risks. QJM 2014; 107 (10): 805-812. doi: 10.1093/qjmed/hcu078

21. Hwang IM, Sun LM, Lin CL, Lee CF, Kao CH. Periodontal disease and treatment improves oral cancer risk among heavy drinkers. Oral Oncology 2001; 37 (2): 153-158. doi: 10.1016/S1368-8375(00)00076-2

22. Chung SD, Tsai MC, Huang CC, Kao LT, Chen CH. A population-based study on the associations between chronic periodontitis and the risk of cancer. International Journal of Clinical Oncology 2016; 21 (2): 219-223. doi: 10.1007/s10147-015-0884-6

23. Hsujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. Annals of Epidemiology 2003; 13 (5): 312-316.